

Supplementary Information for Org. Biomol. Chem.

**Design, Synthesis and Biological evaluation of Thrombin inhibitors based on a
Pyridine Scaffold.**

David Blomberg,[†] Tomas Fex,[#] Yafeng Xue,[#] Kay Brickmann,[#] and Jan Kihlberg^{†#*}

[†]*Organic Chemistry, Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden*

and [#]AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden.

jan.kihlberg@chem.umu.se

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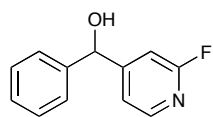
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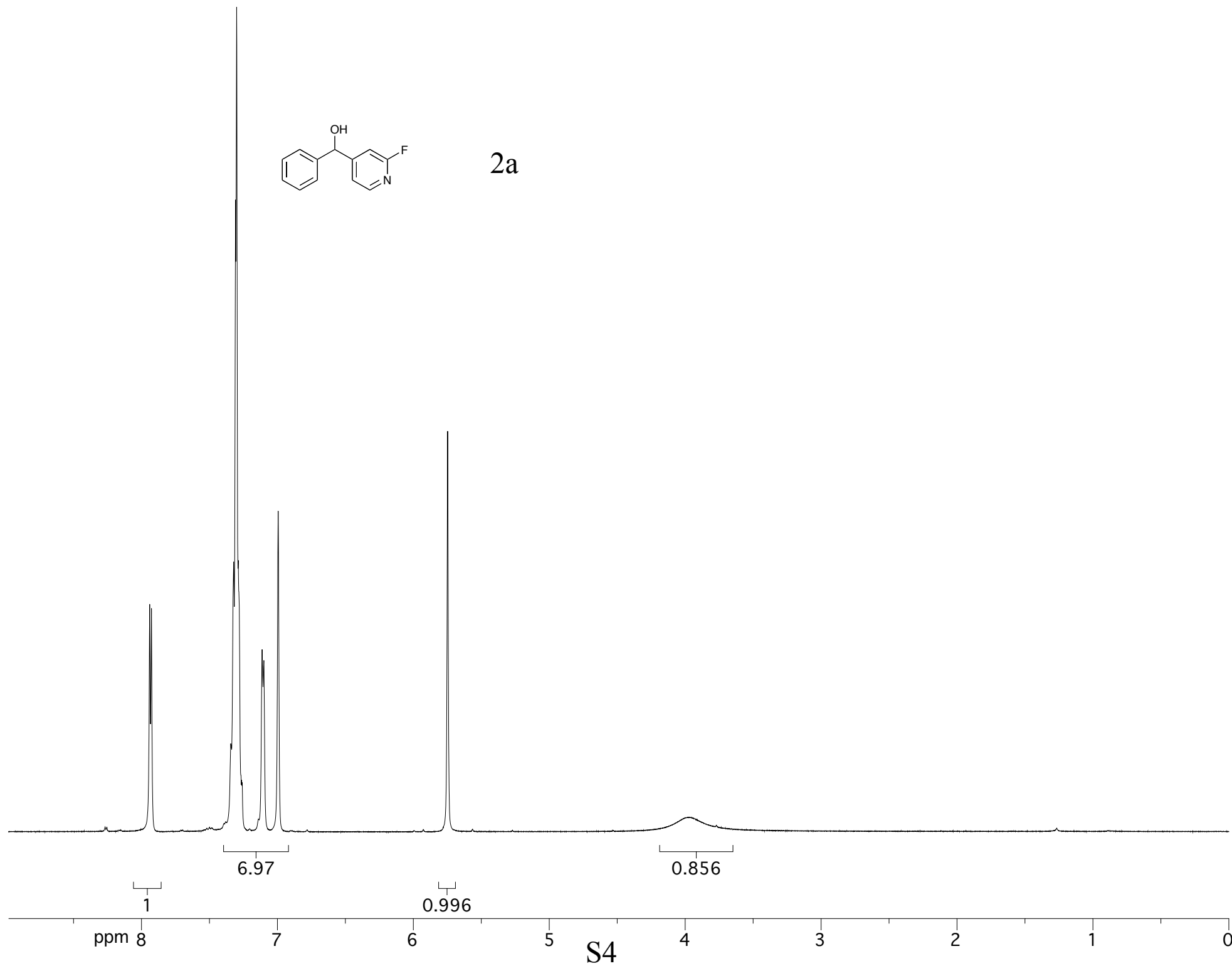
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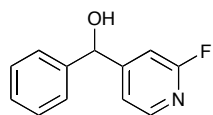
S20: ¹H NMR for compound 8a

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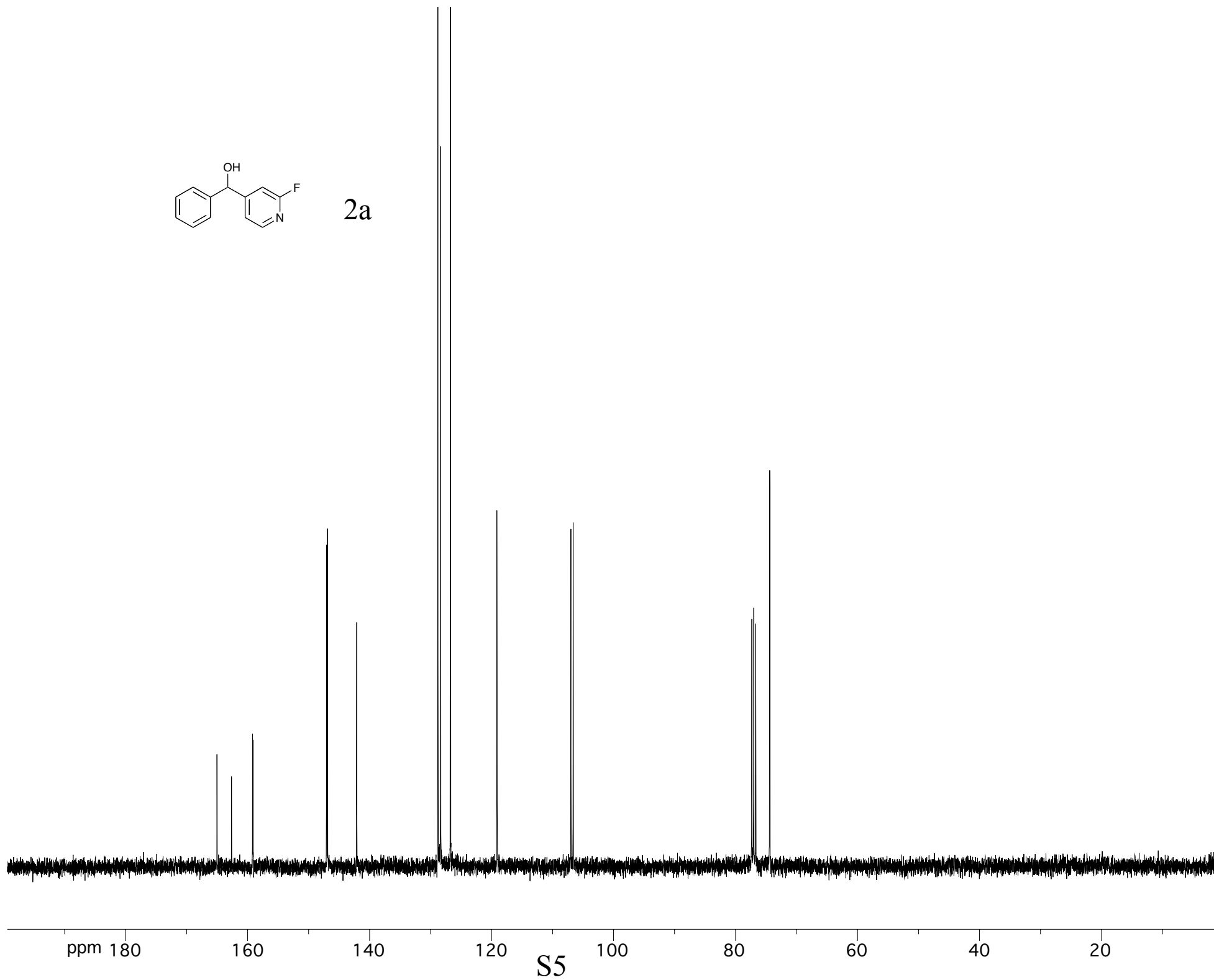


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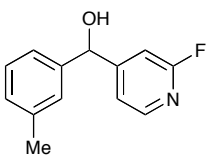
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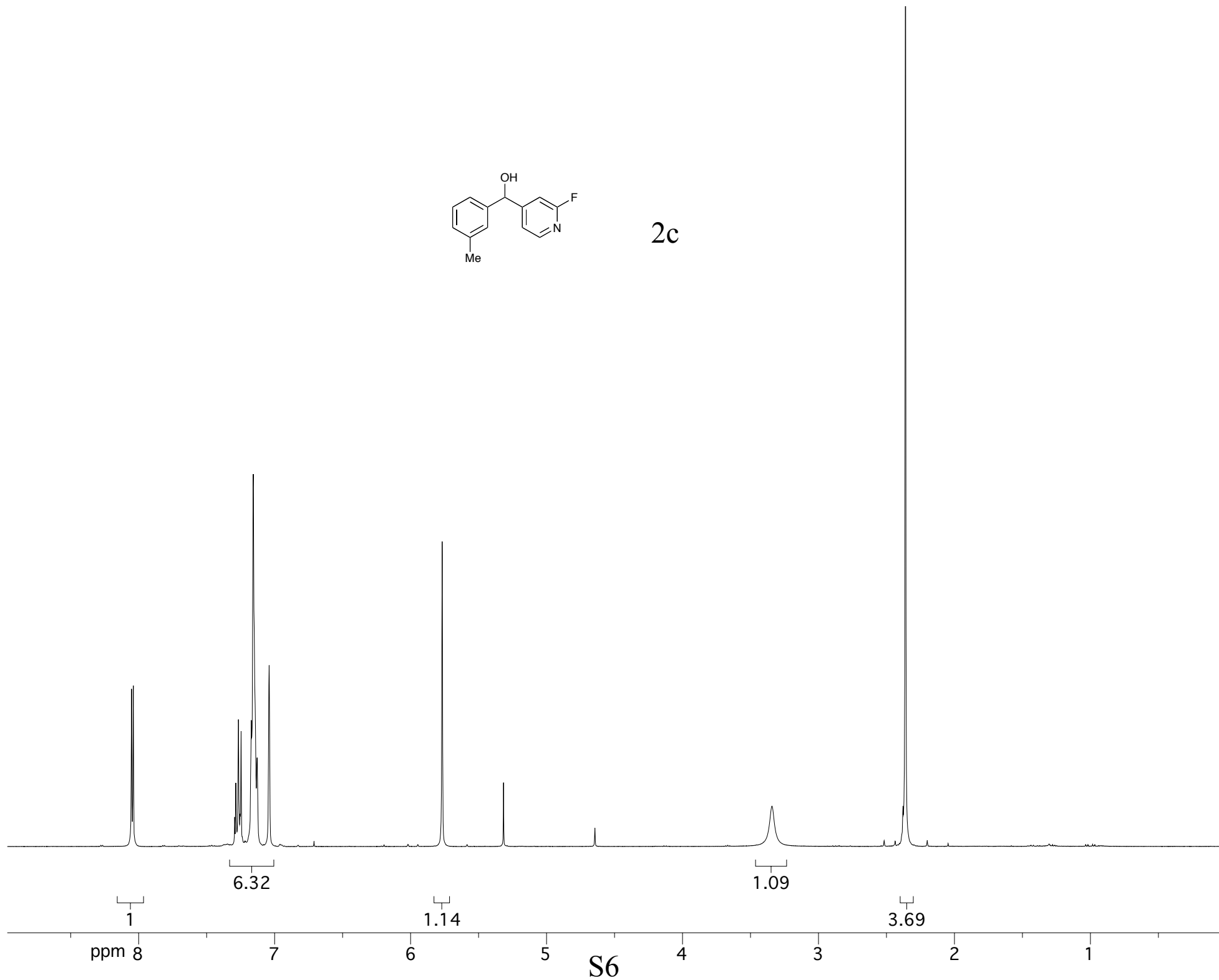
General methods and materials: ^1H and ^{13}C NMR were recorded in CDCl_3 at 305 K, residual CHCl_3 ($\delta = 7.27$) or CDCl_3 ($\delta = 77.0$) and CD_3OD residual CD_2HOD ($\delta = 3.35$) or CD_3OD ($\delta = 48.0$) as internal standards. ^1H NMR and ^{13}C NMR spectra for all isolated compounds are presented in the supporting information along with analytical chromatograms for compounds **20a-c** run on a C18 column with A (95% CH_3CN + 5% buffer solution)/B (100% buffer solution, water containing 0.1 M ammonium acetate) as eluents with a gradient running from 0→100% A in B over 60 minutes. Preparative HPLC was run with the same eluents on a C18 column but the gradient was run from 0→100% A in B over 50 minutes. All microwave irradiation were performed in a Smith Creator single node instrument with EmrysTM process vials (2-5 mL), with temperature measurement by infrared detection. Fixed hold time was always used, with a ramp time of 1-2 min. All organic extracts were dried over Na_2SO_4 unless otherwise stated.

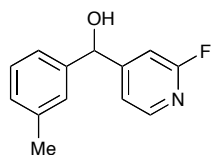
References

- (1) Brickmann, K.; Yuan, Z.; Sethson, I.; Somfai, P.; Kihlberg, J. *Chem. Eur. J.* **1999**, *5*, 2241-2253.
- (2) Yuan, Z.; Blomberg, D.; Sethson, I.; Brickmann, K.; Ekholm, K.; Johansson, B.; Nilsson, A.; Kihlberg, J. *J. Med. Chem.* **2002**, *45*, 2512-2519.

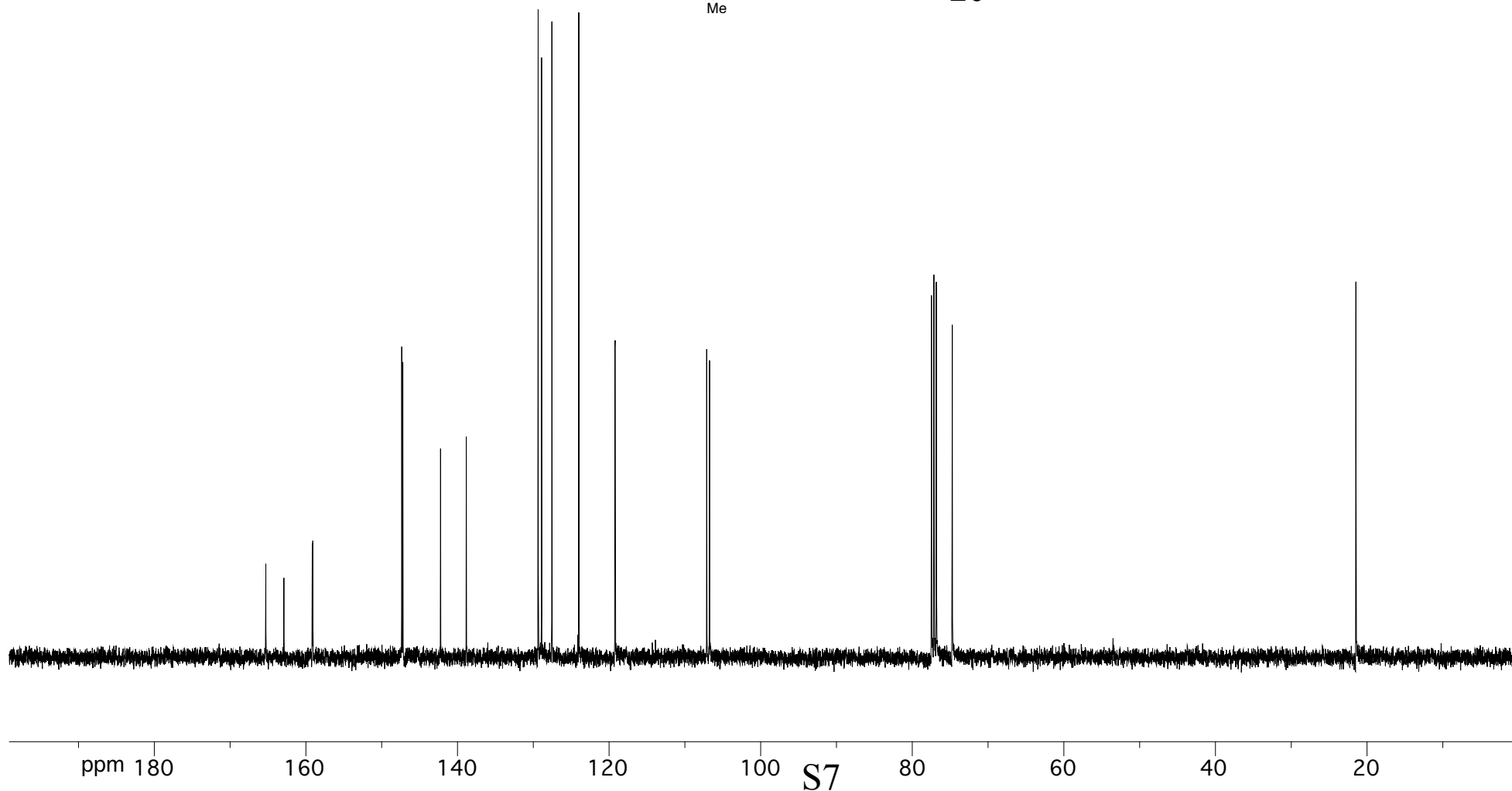


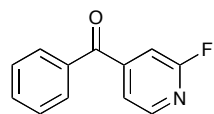
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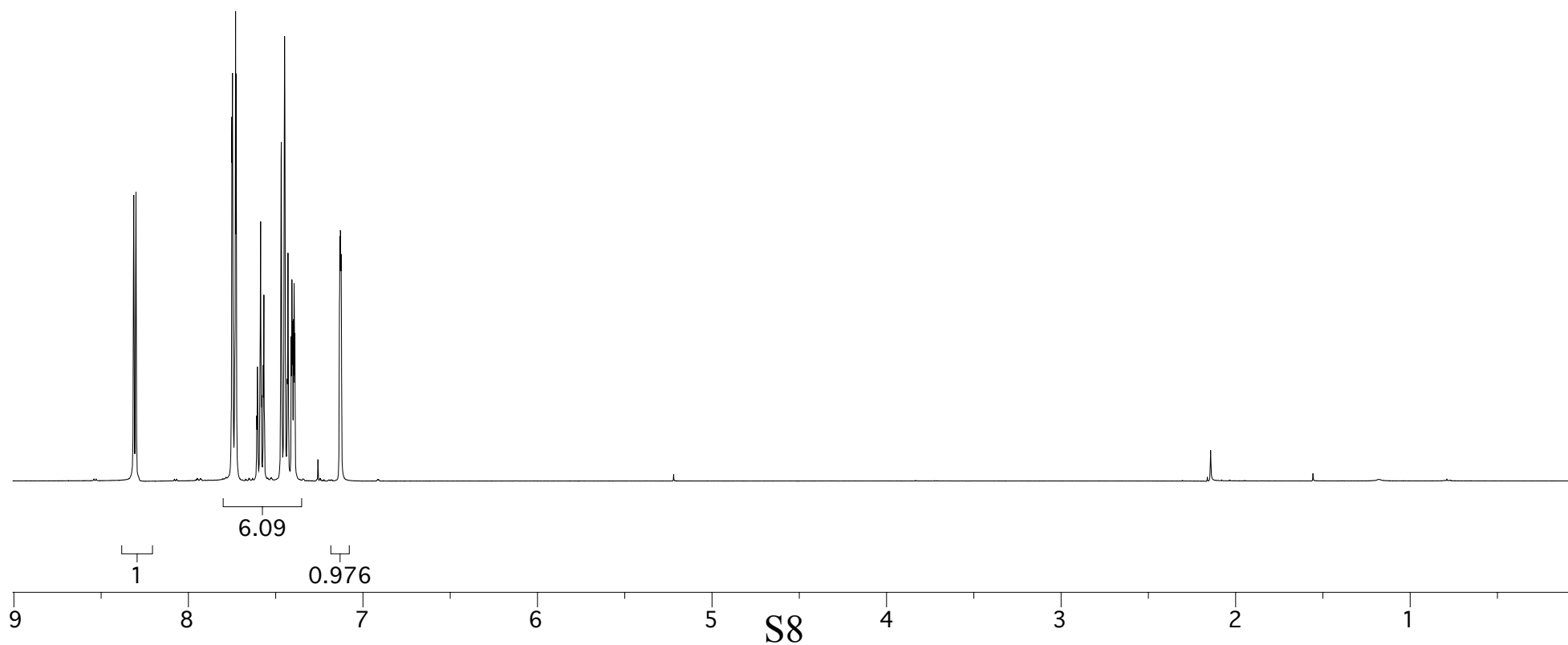


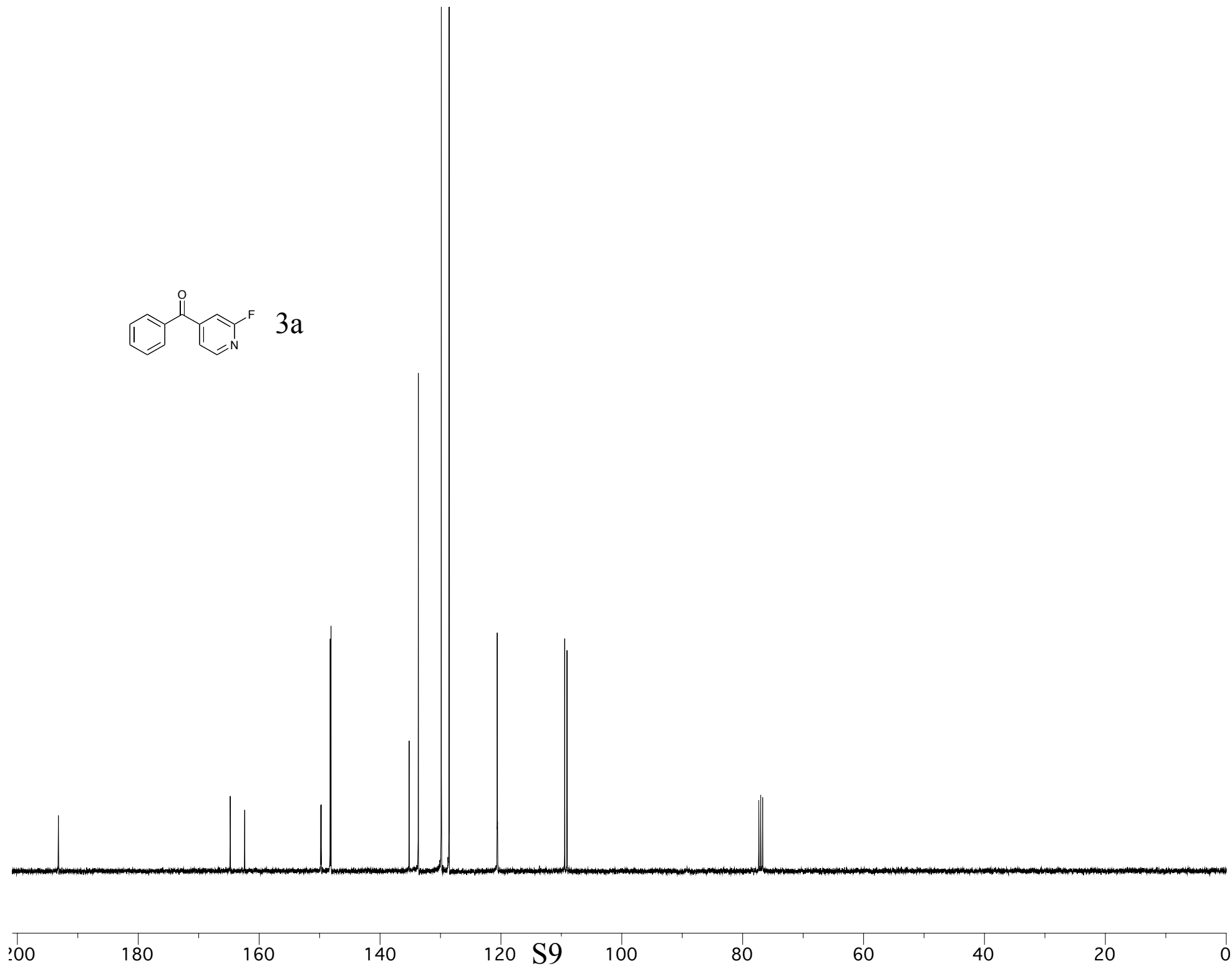
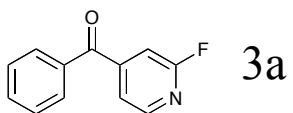
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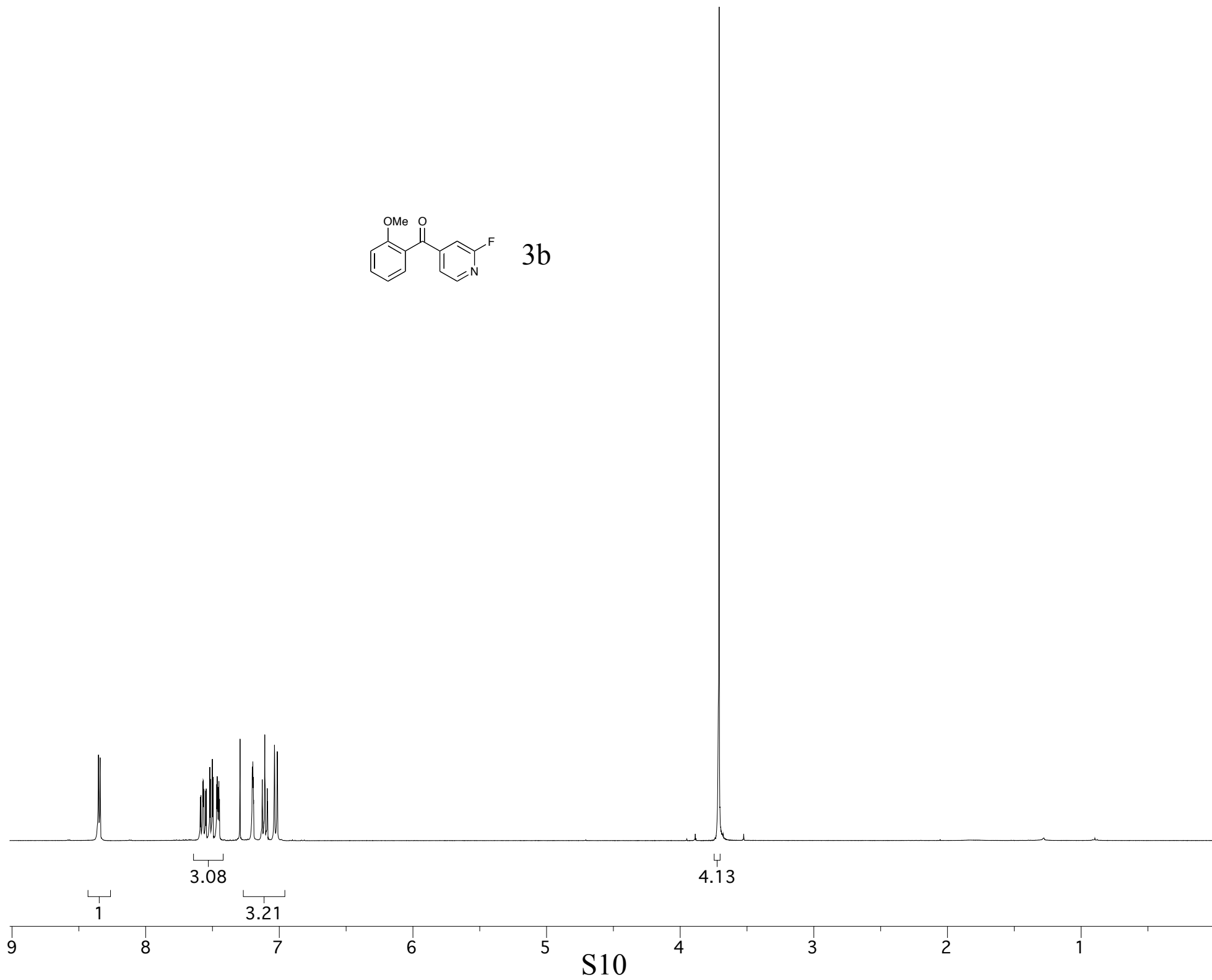
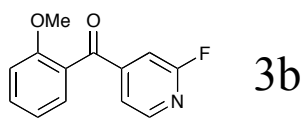


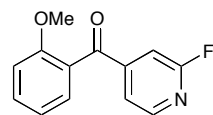


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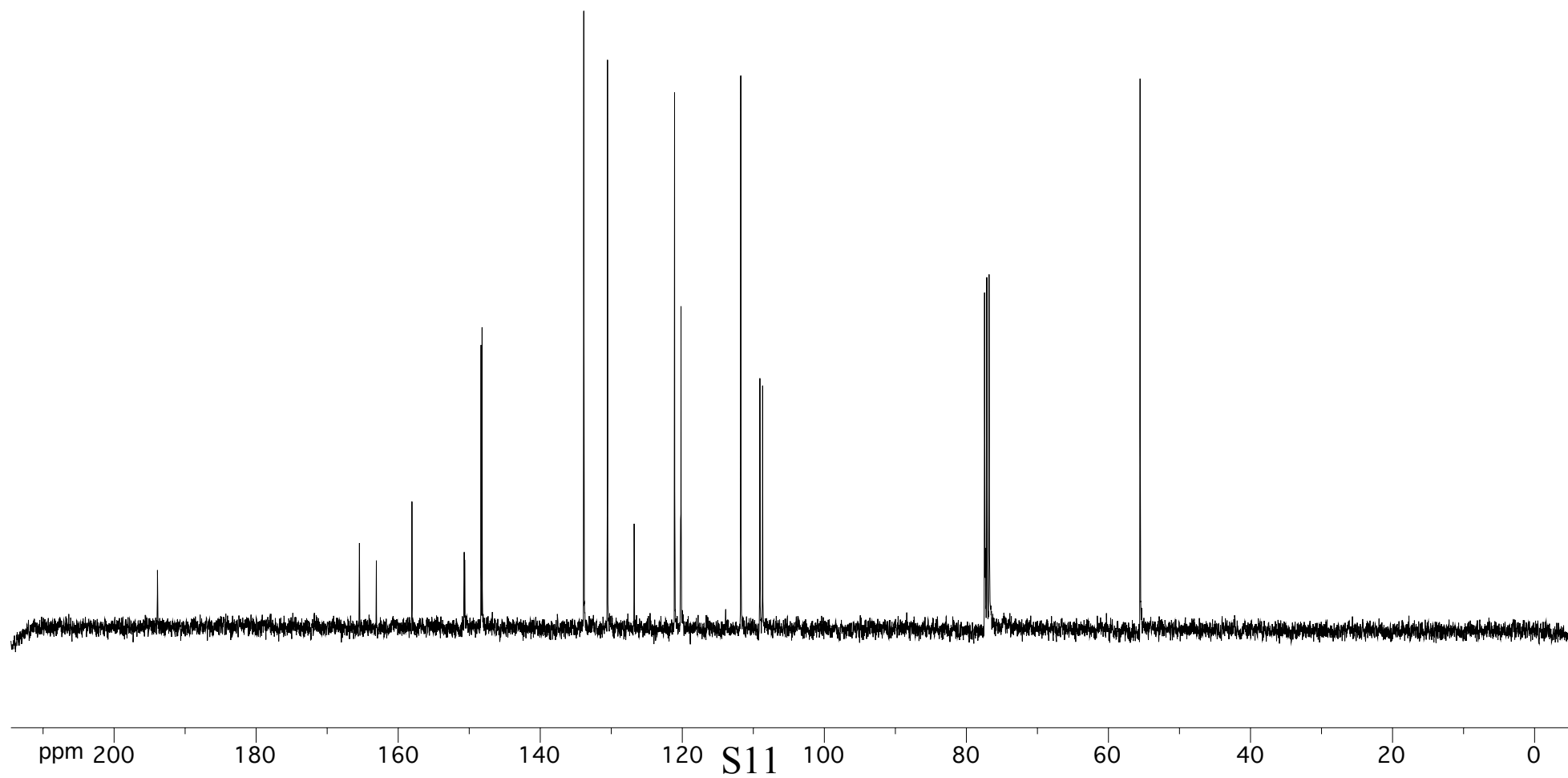


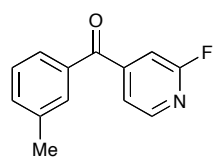




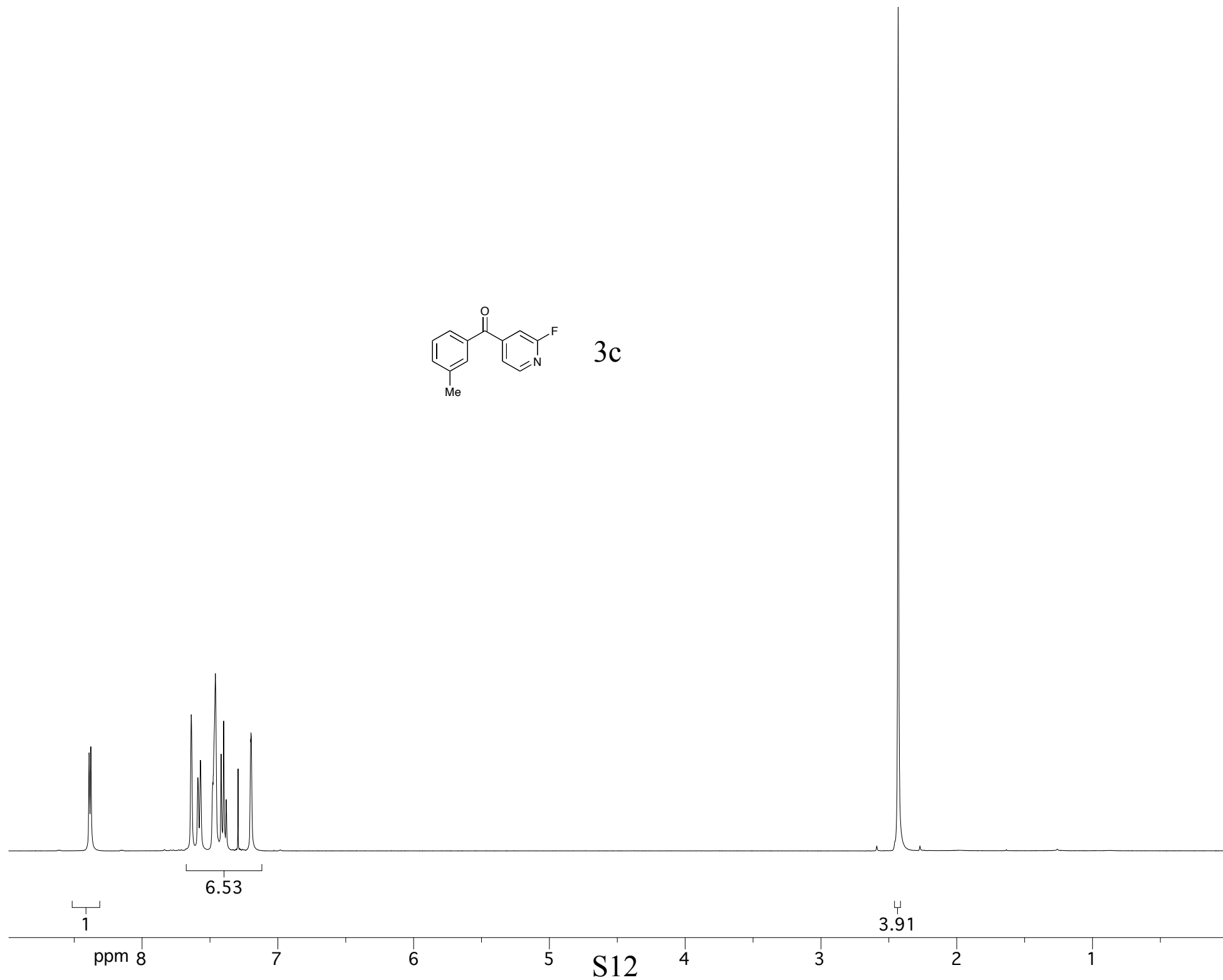


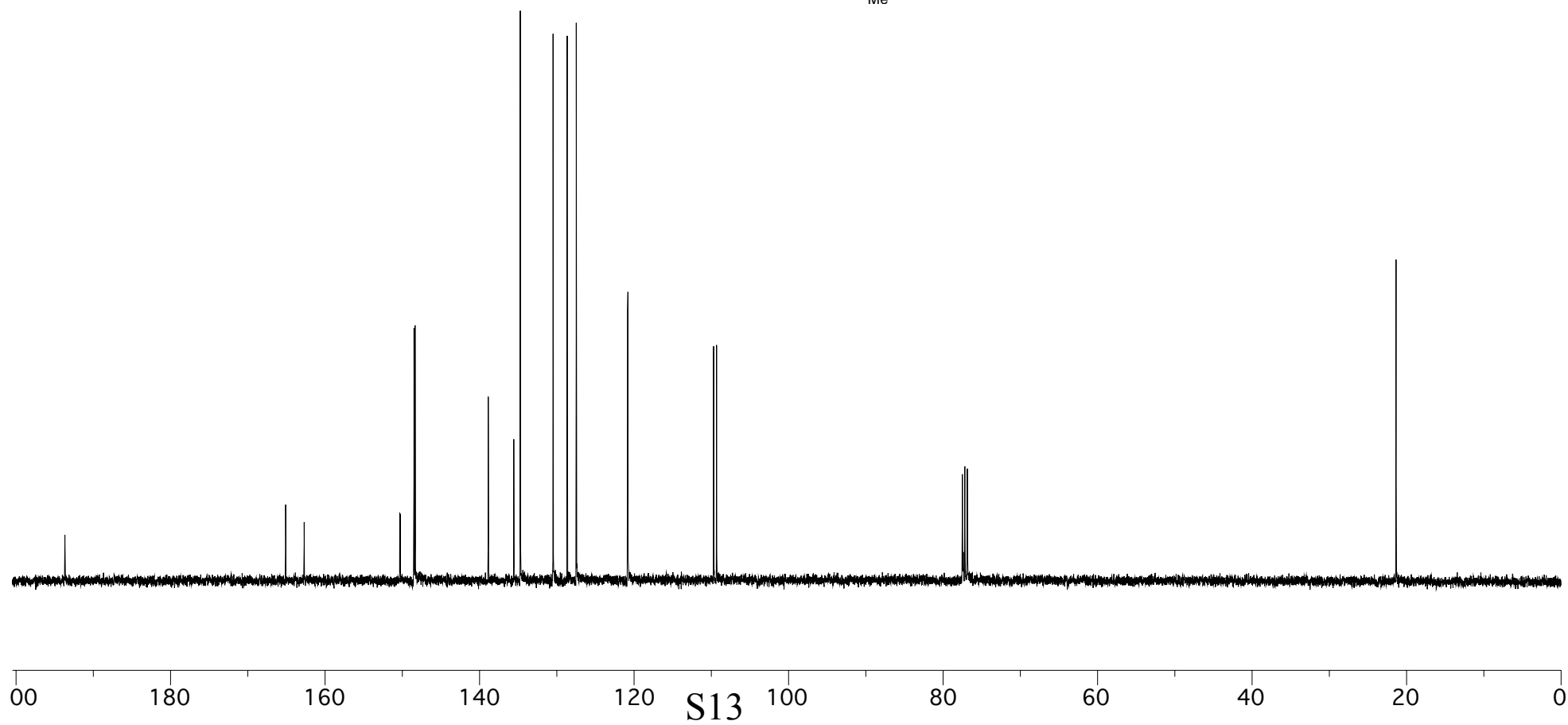
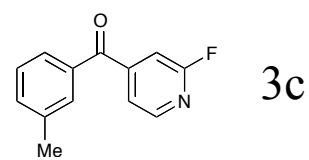
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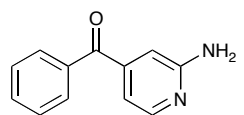




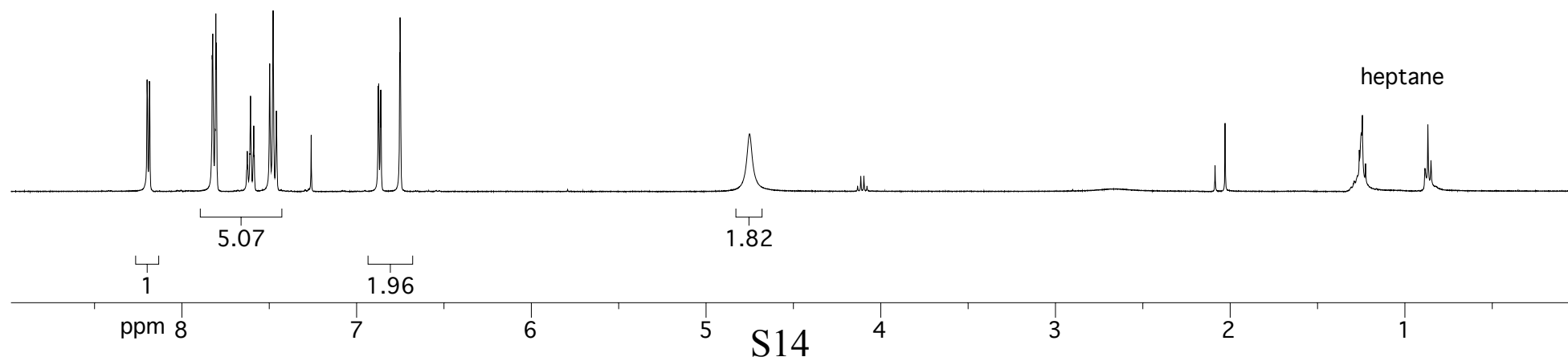
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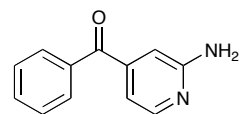




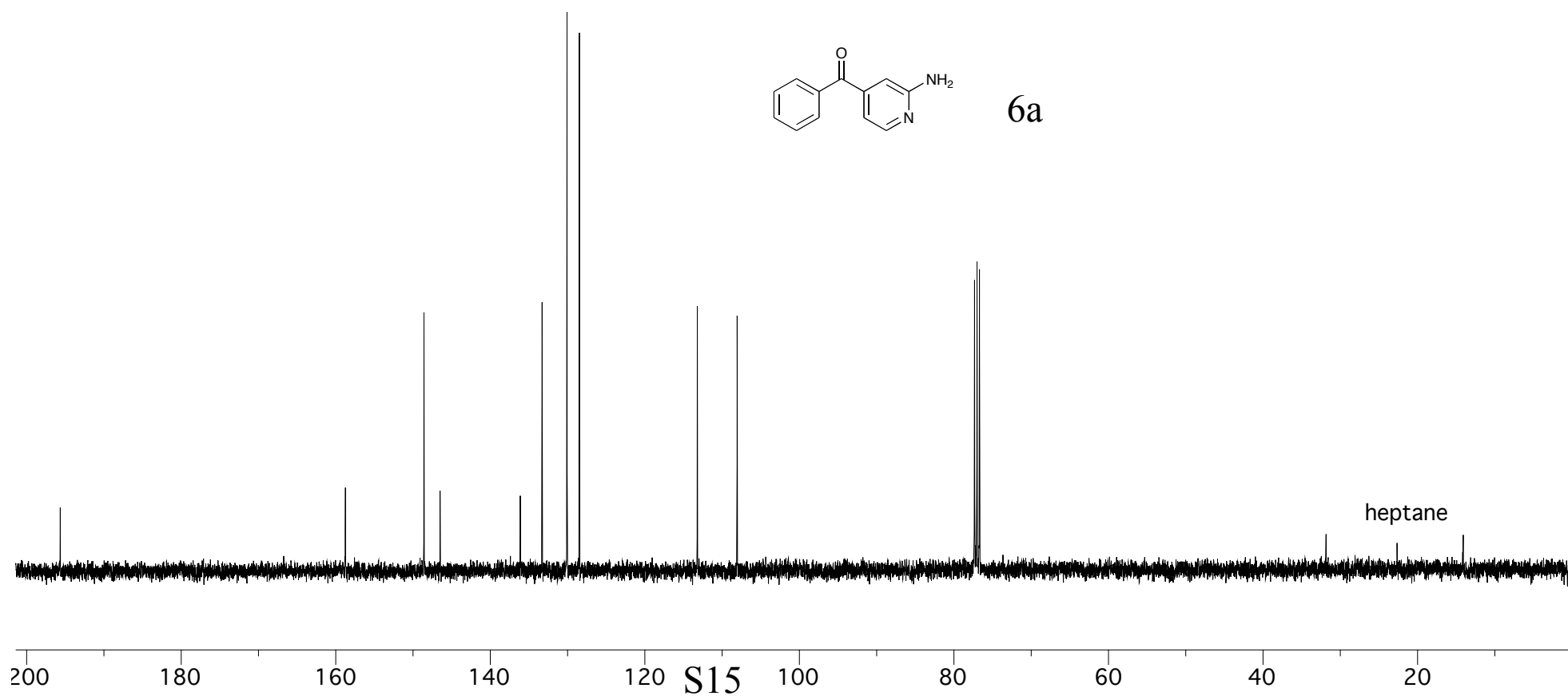


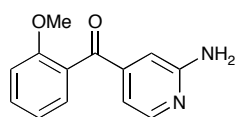
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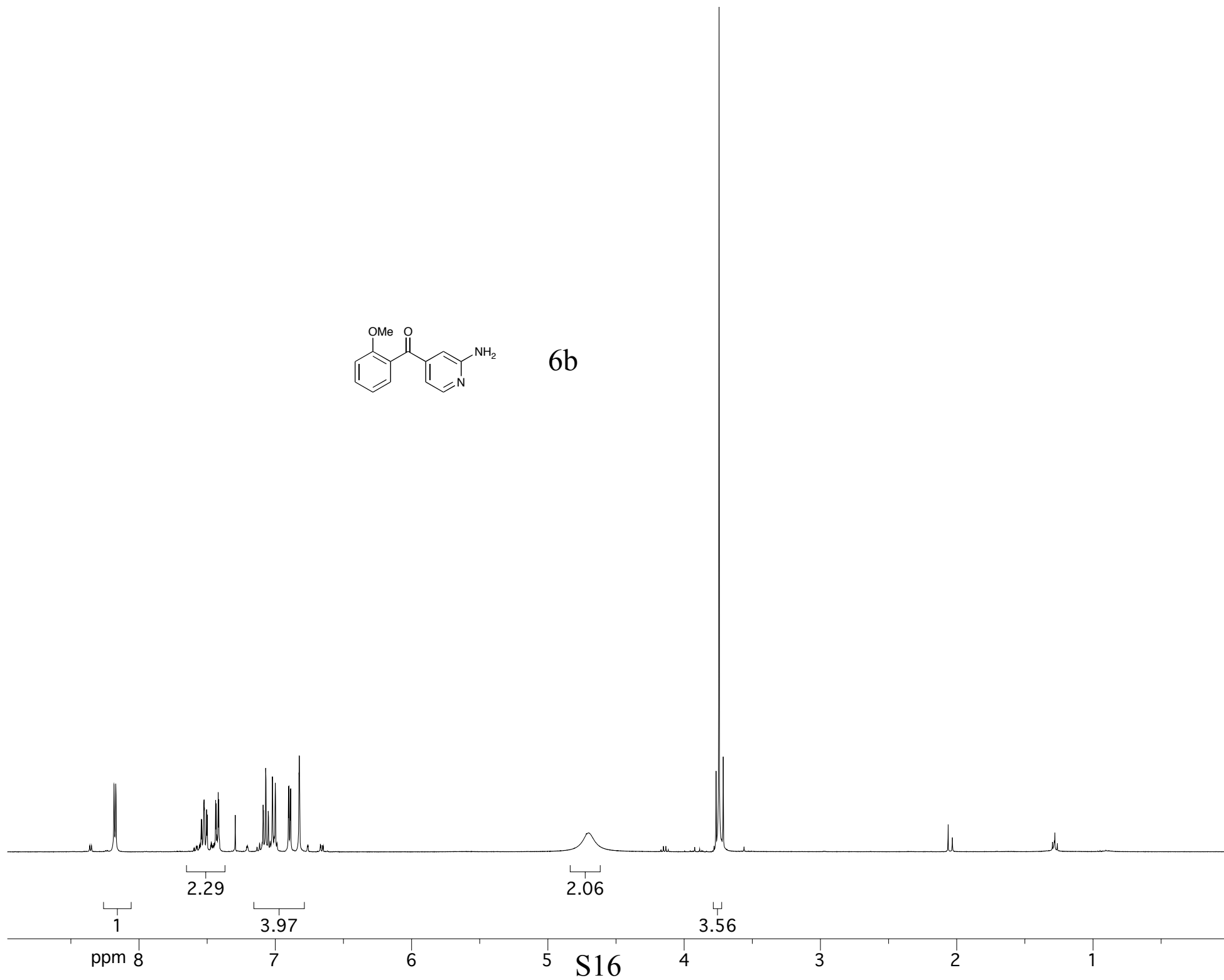


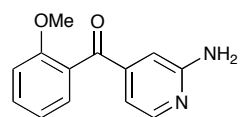
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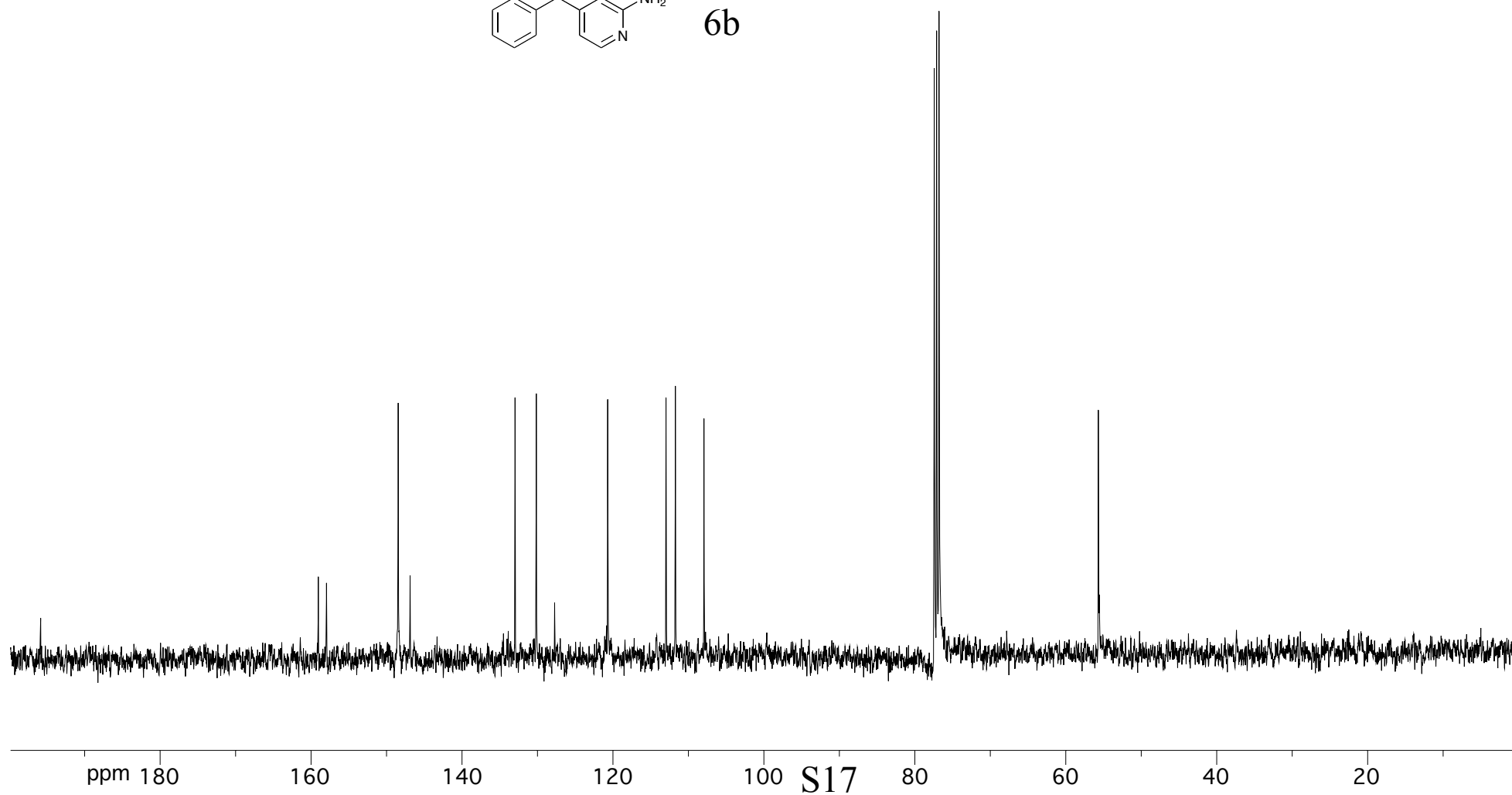


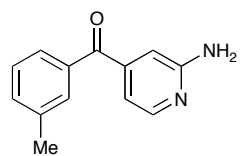
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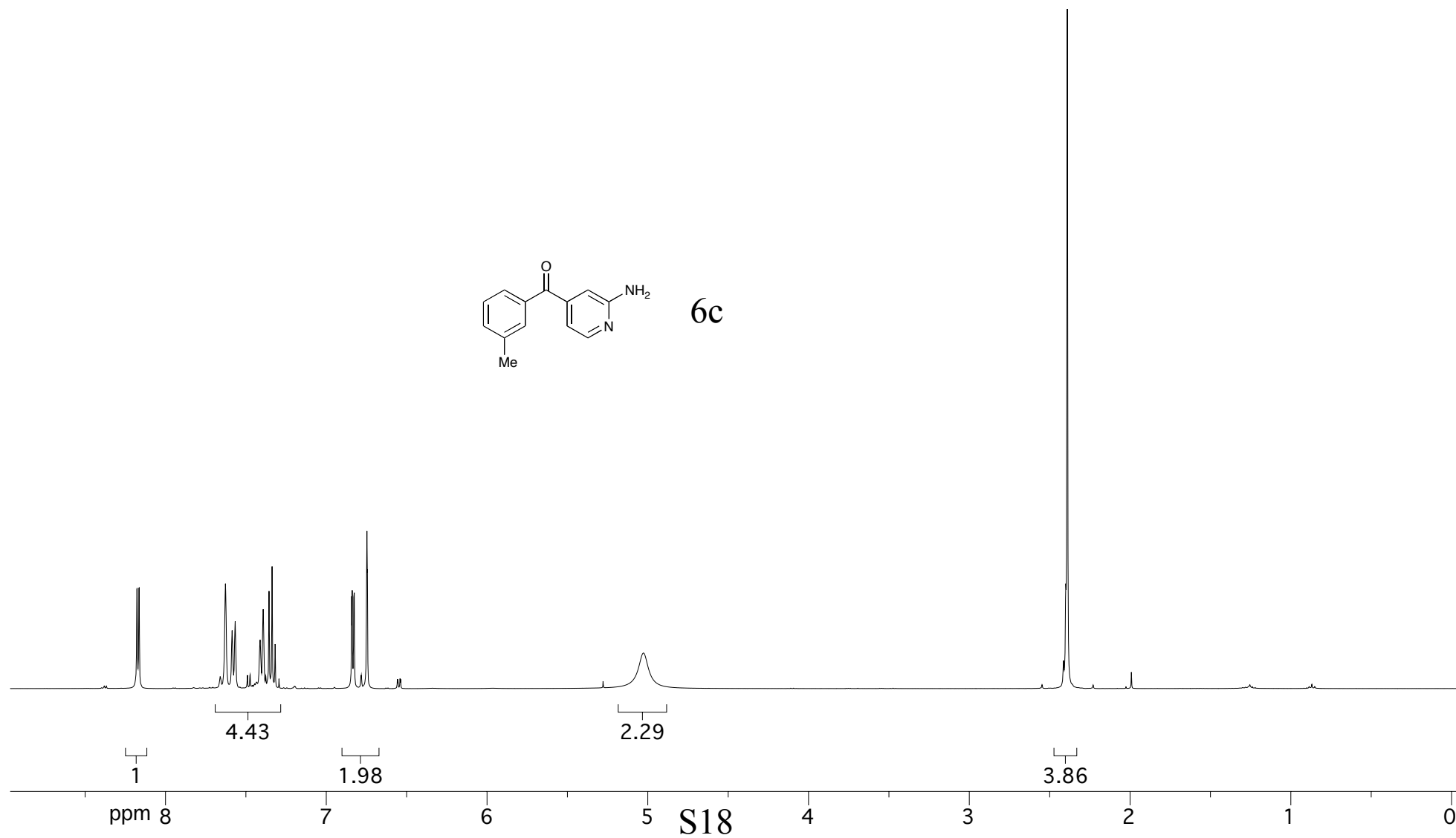


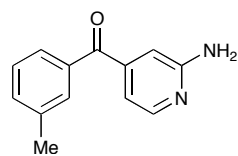
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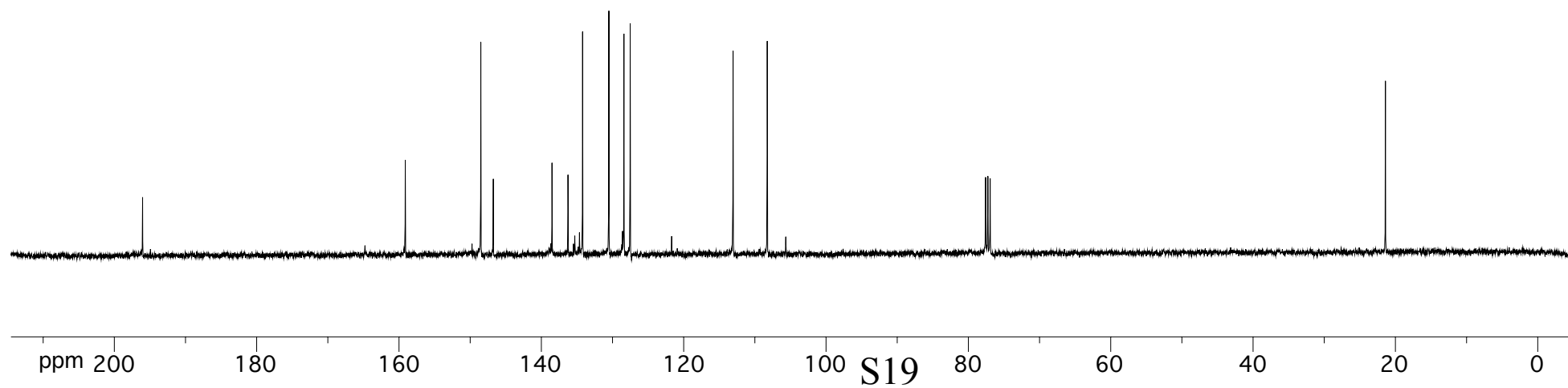


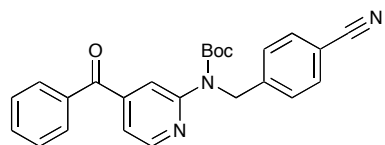
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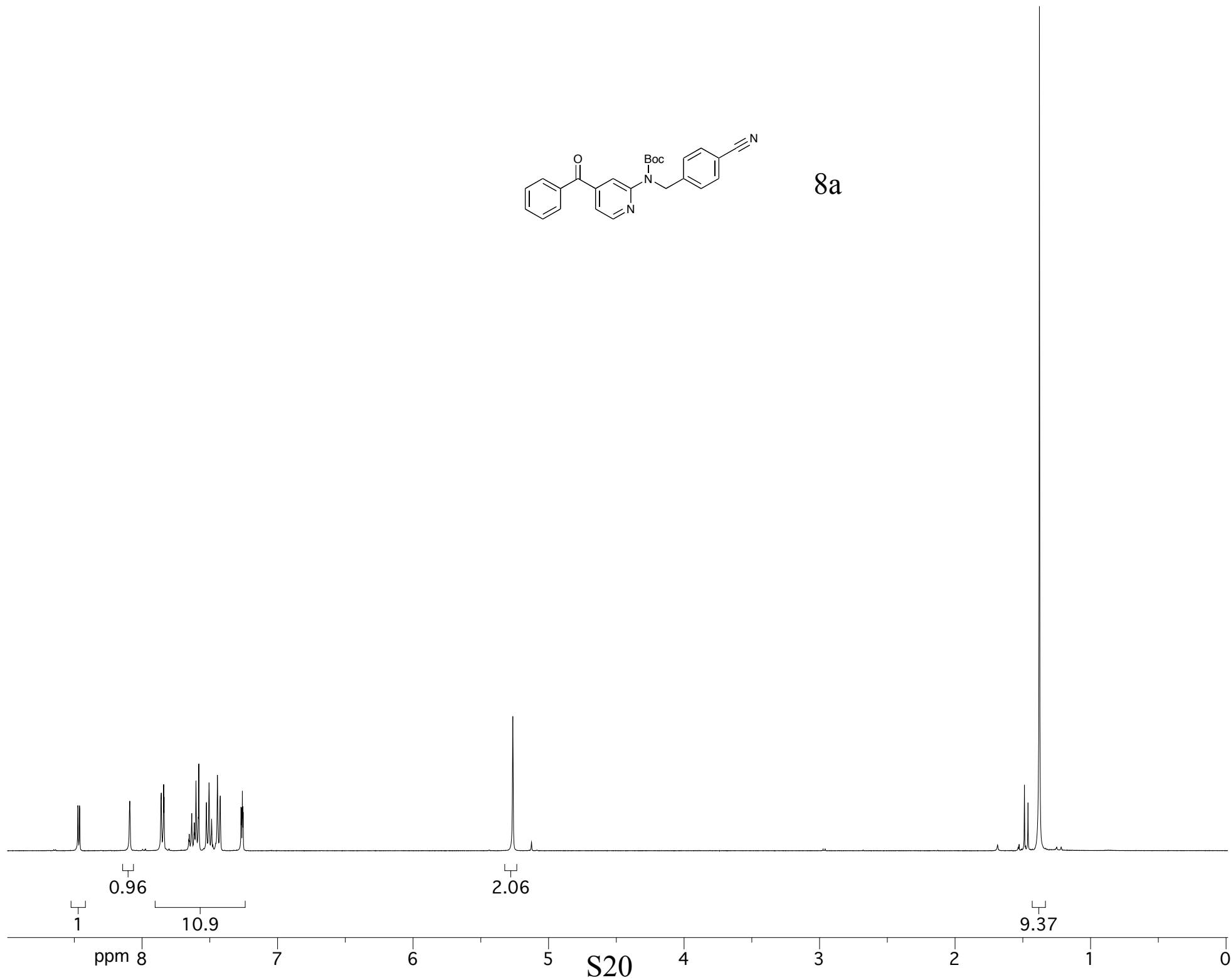


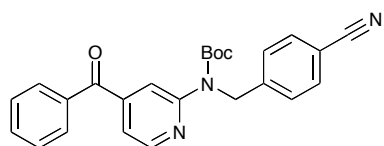
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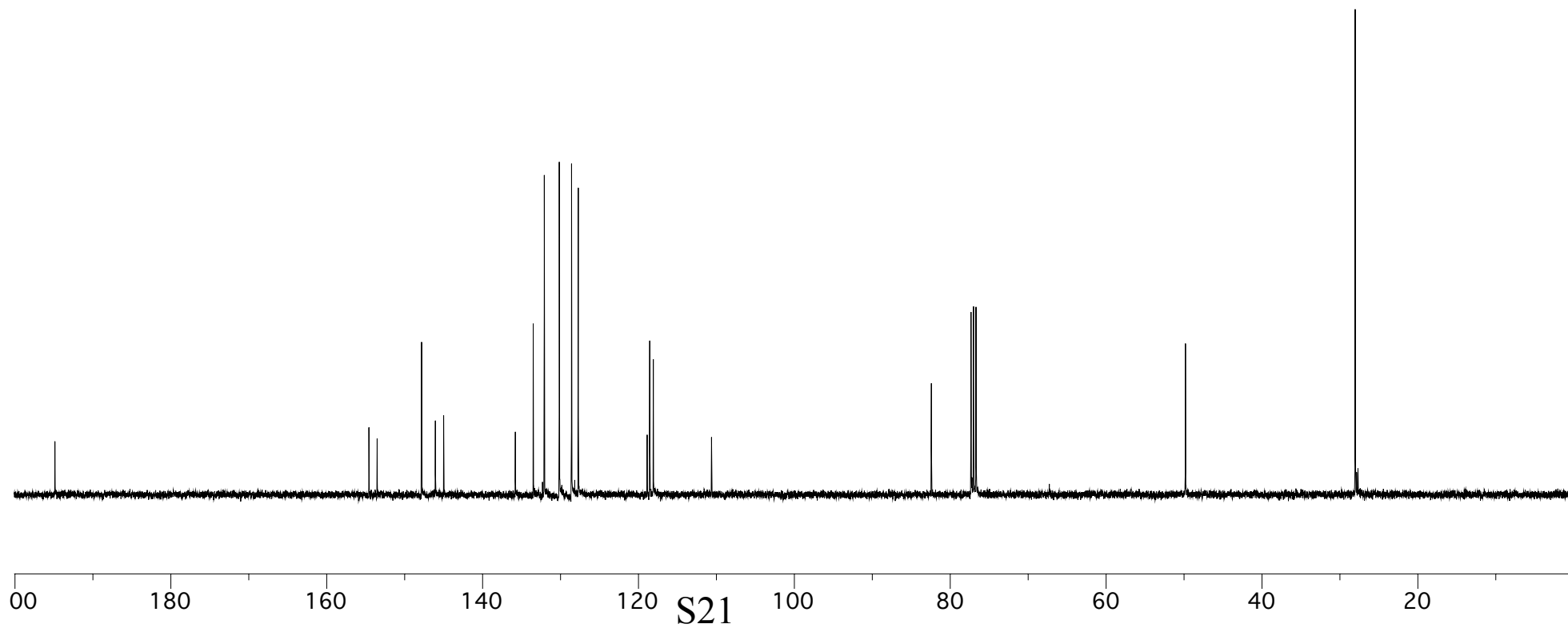


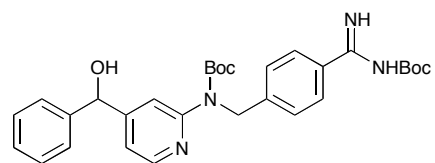
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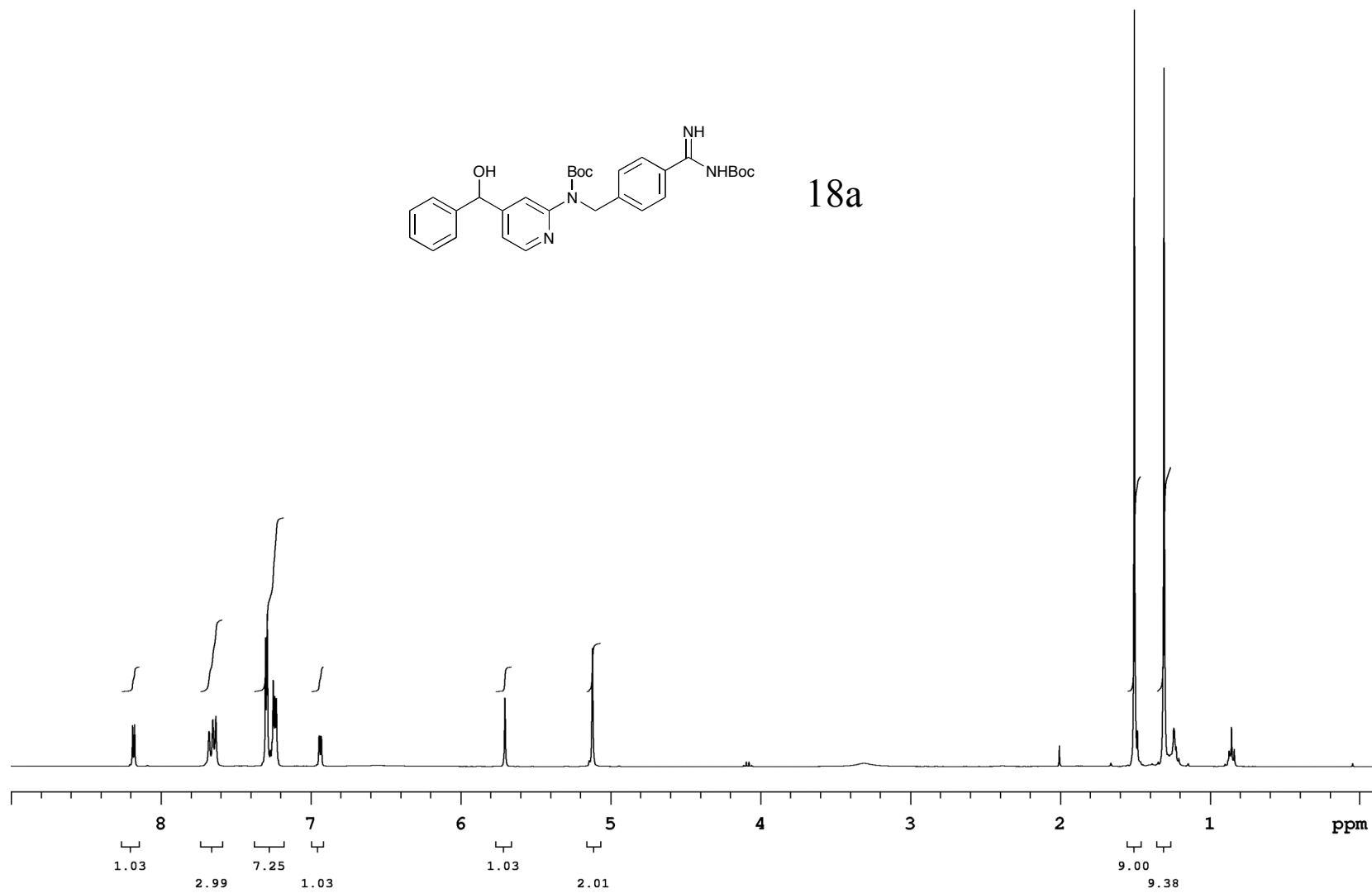


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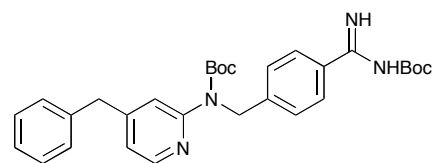


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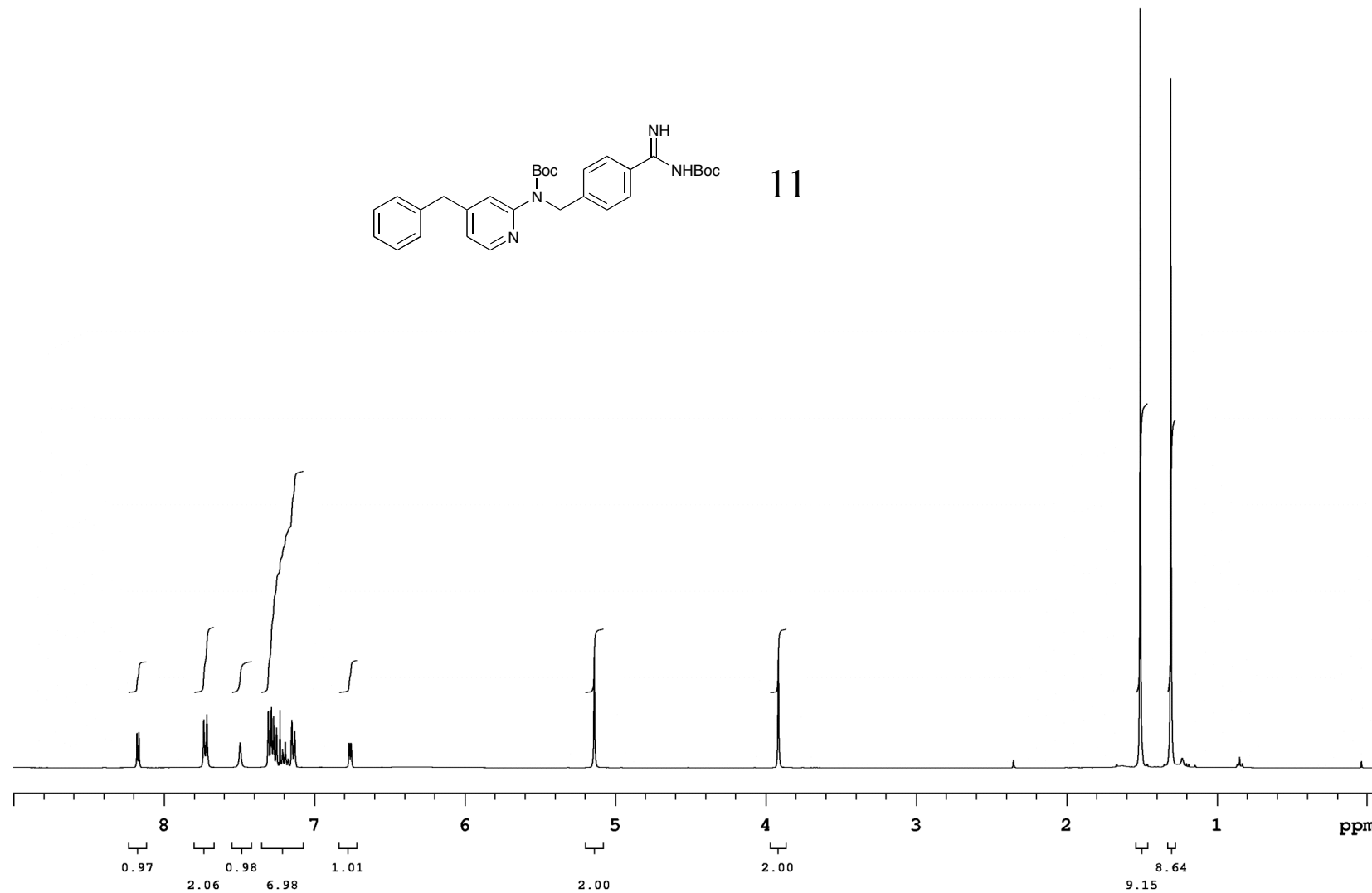


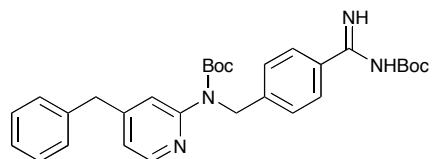
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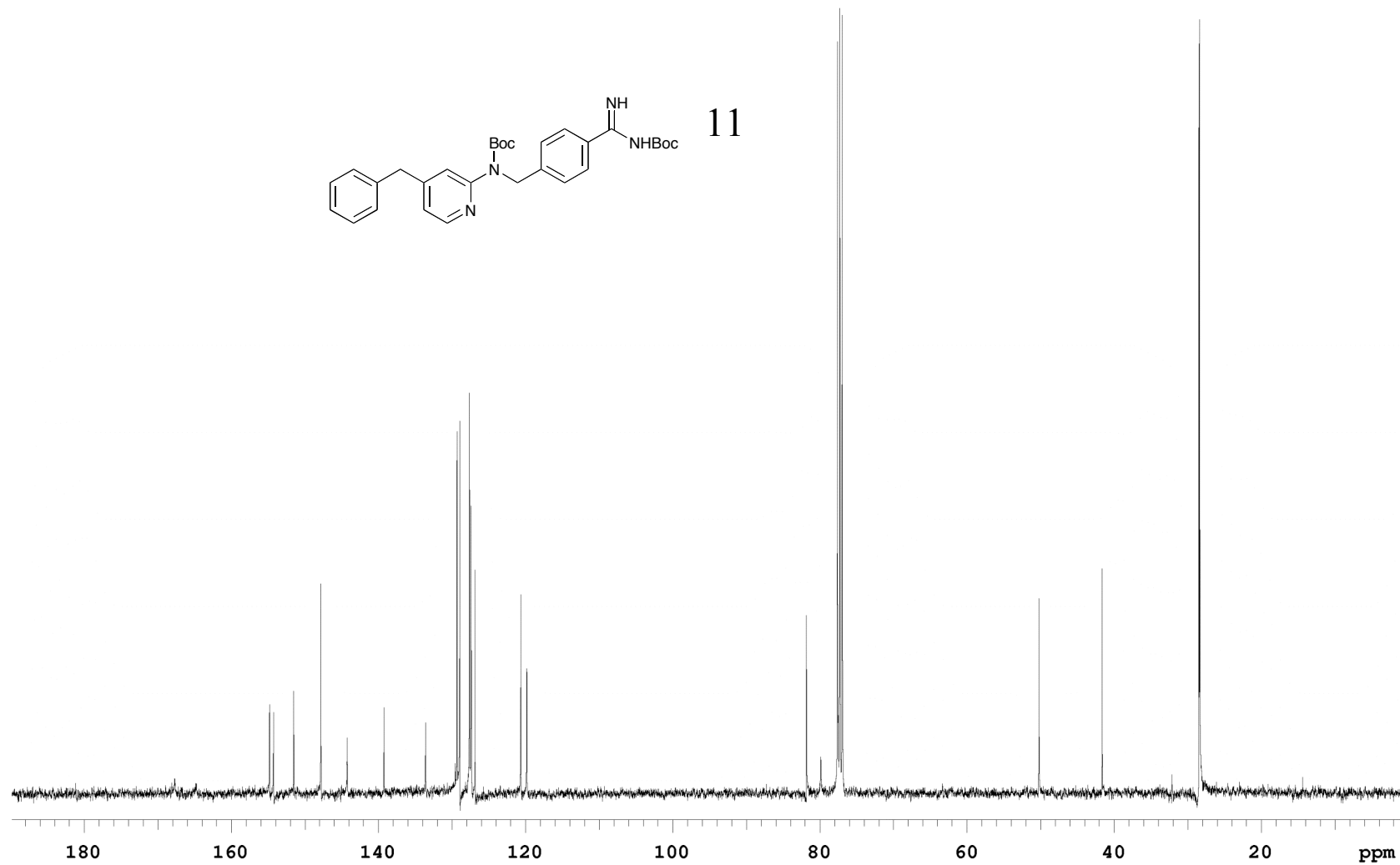


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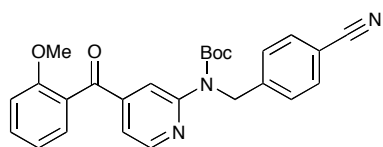




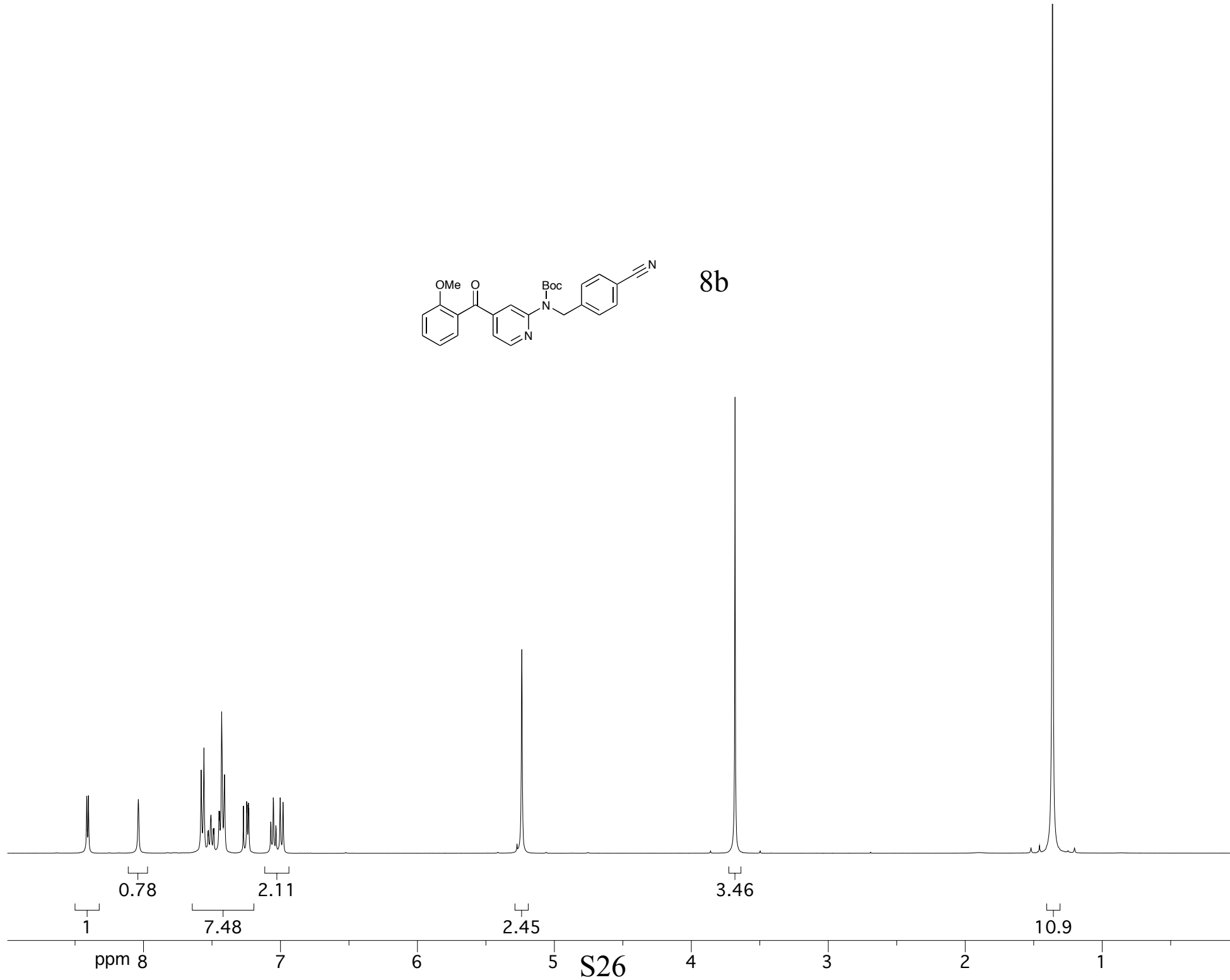
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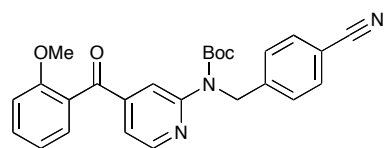


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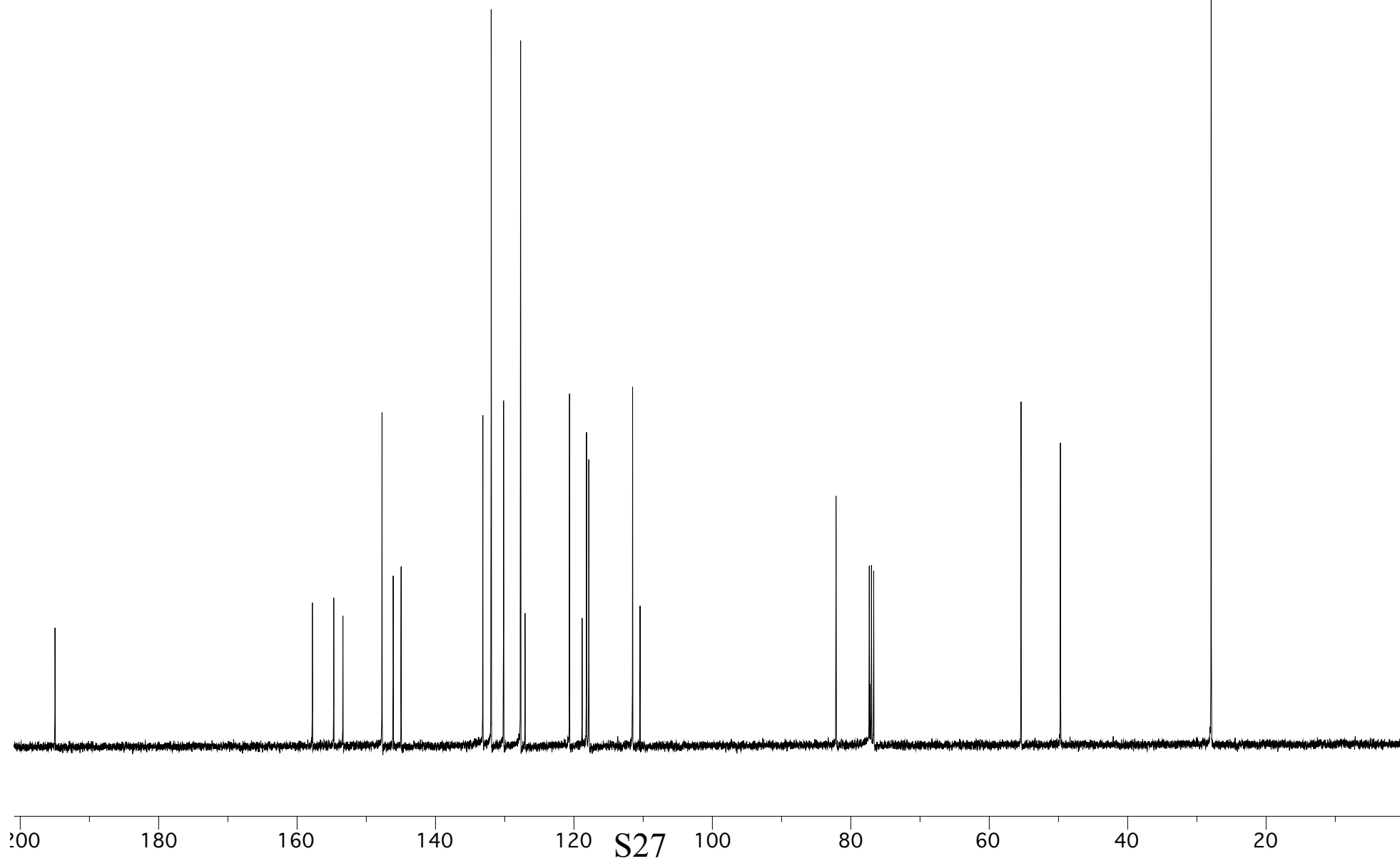


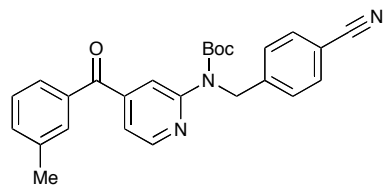
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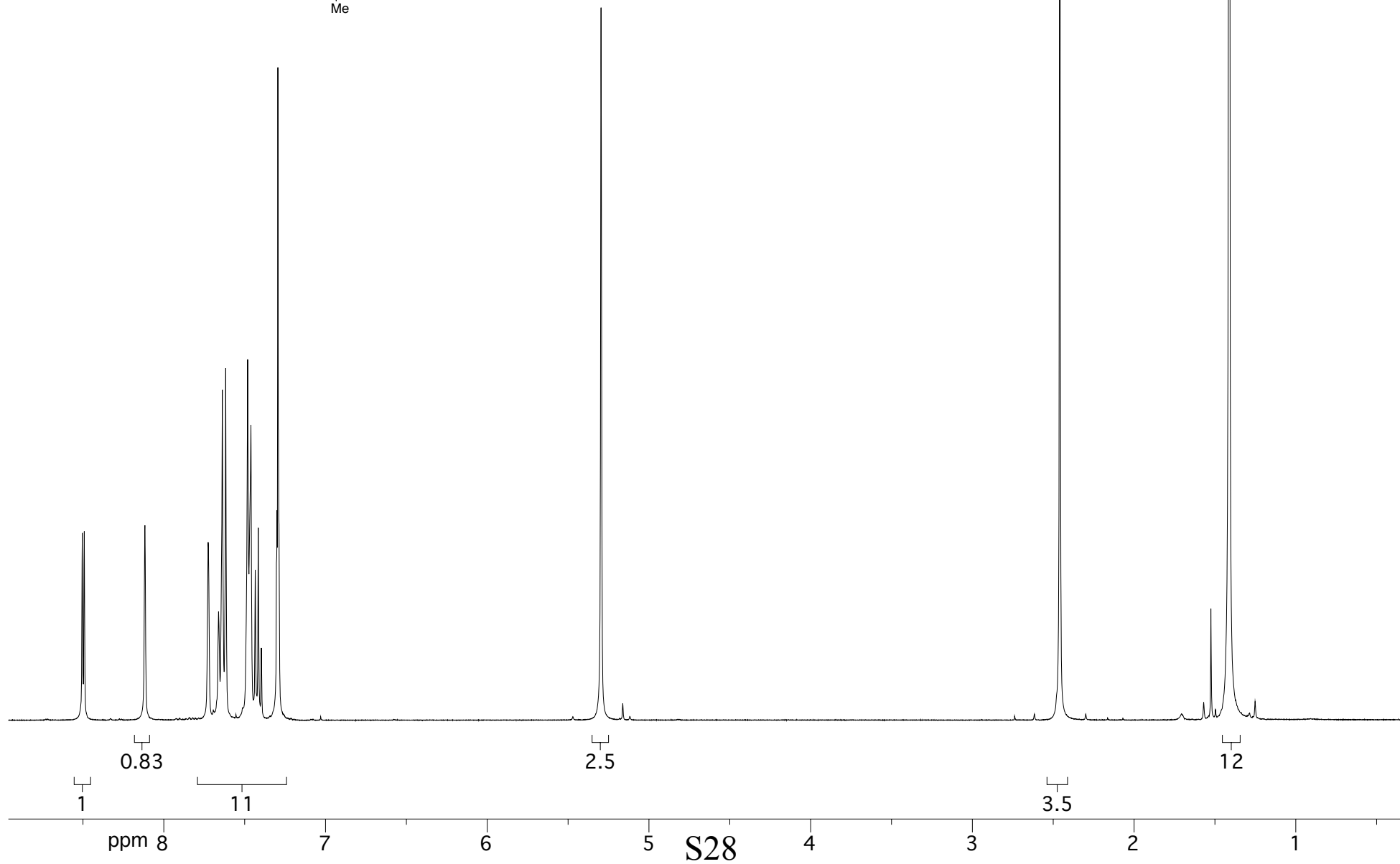


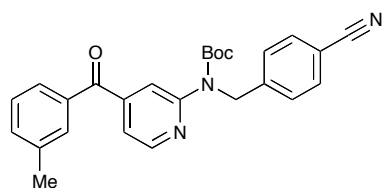
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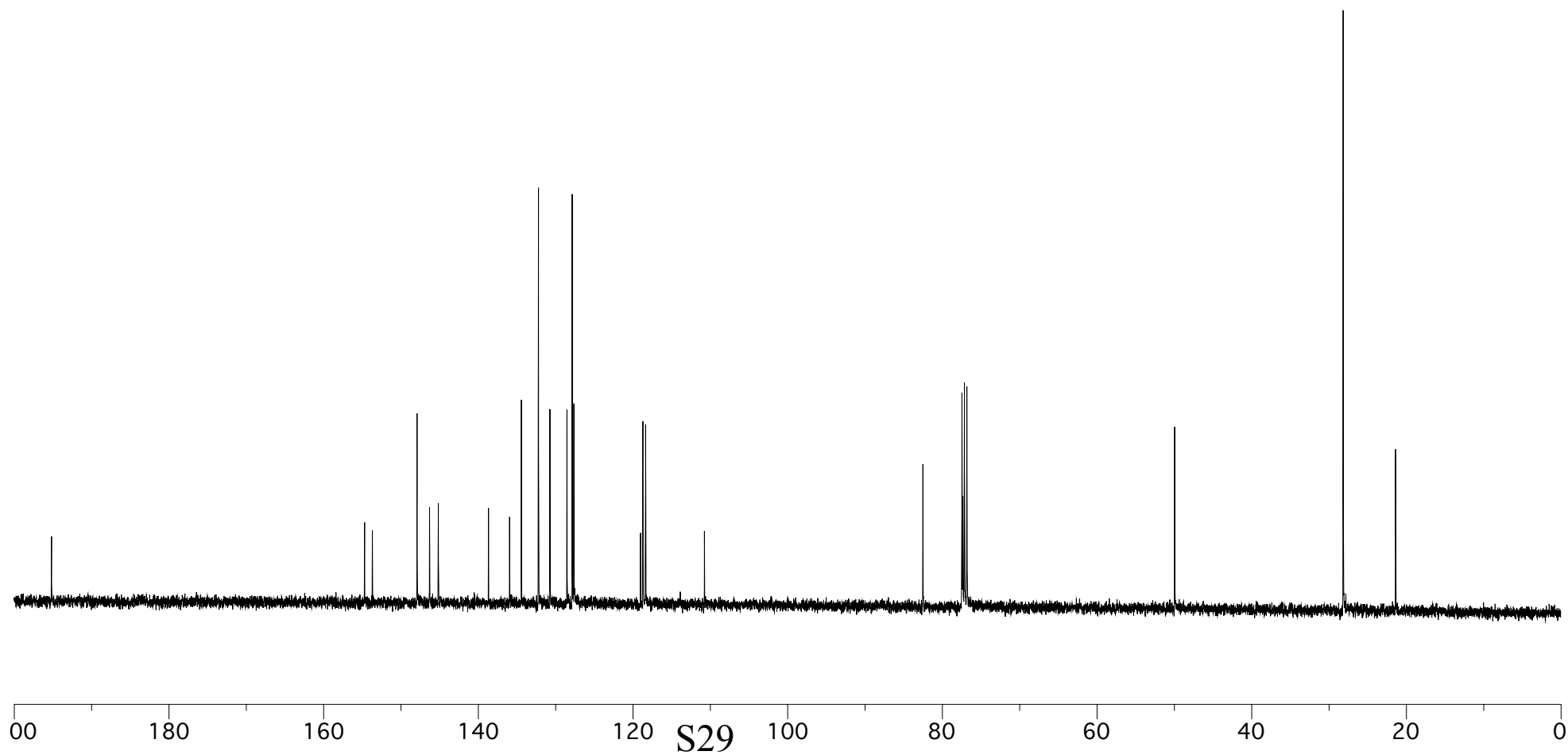


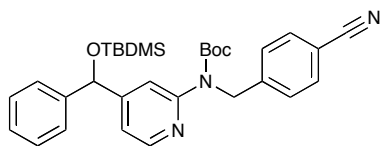
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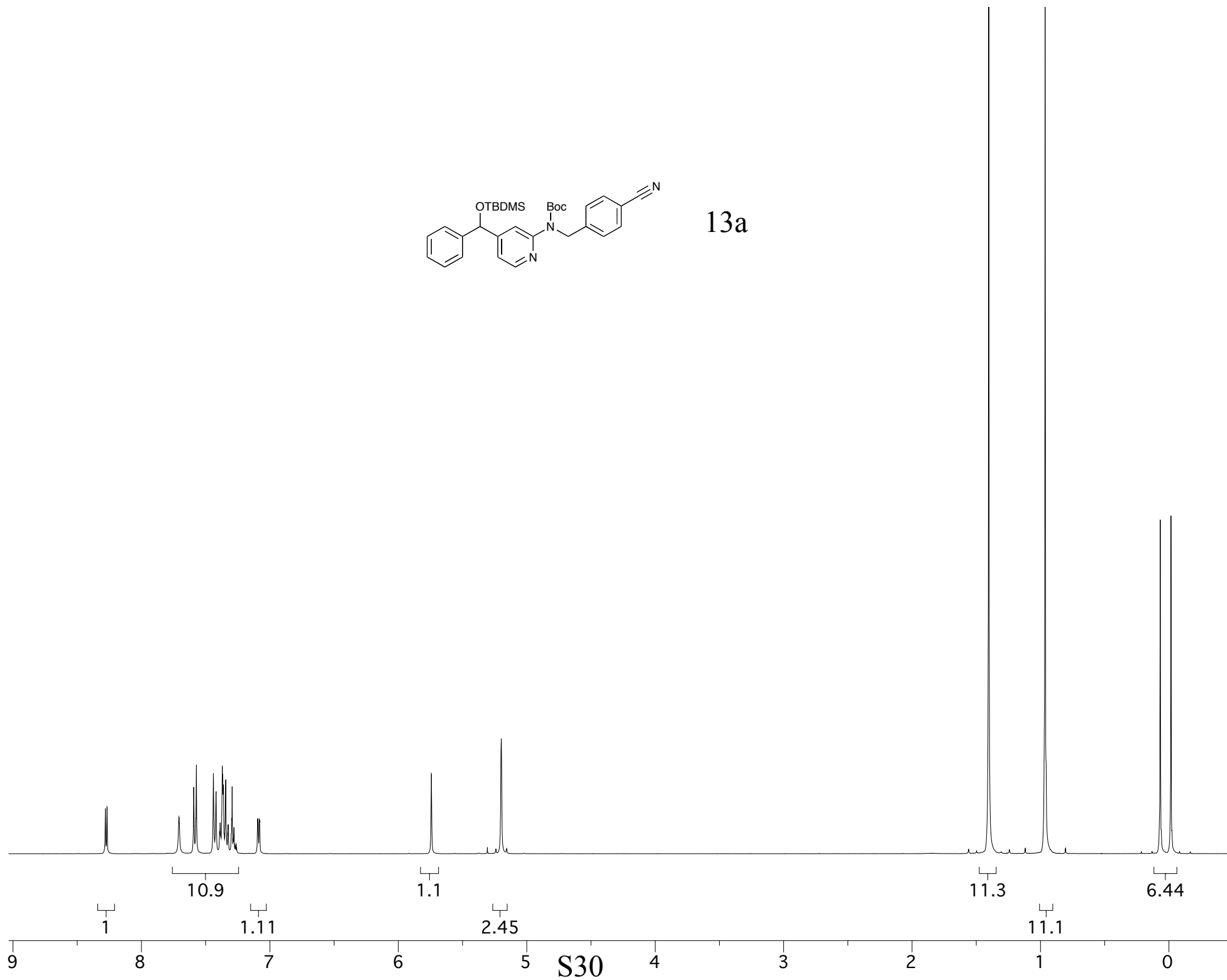


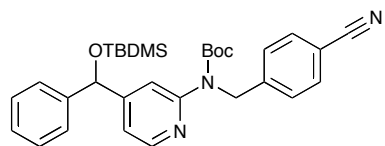
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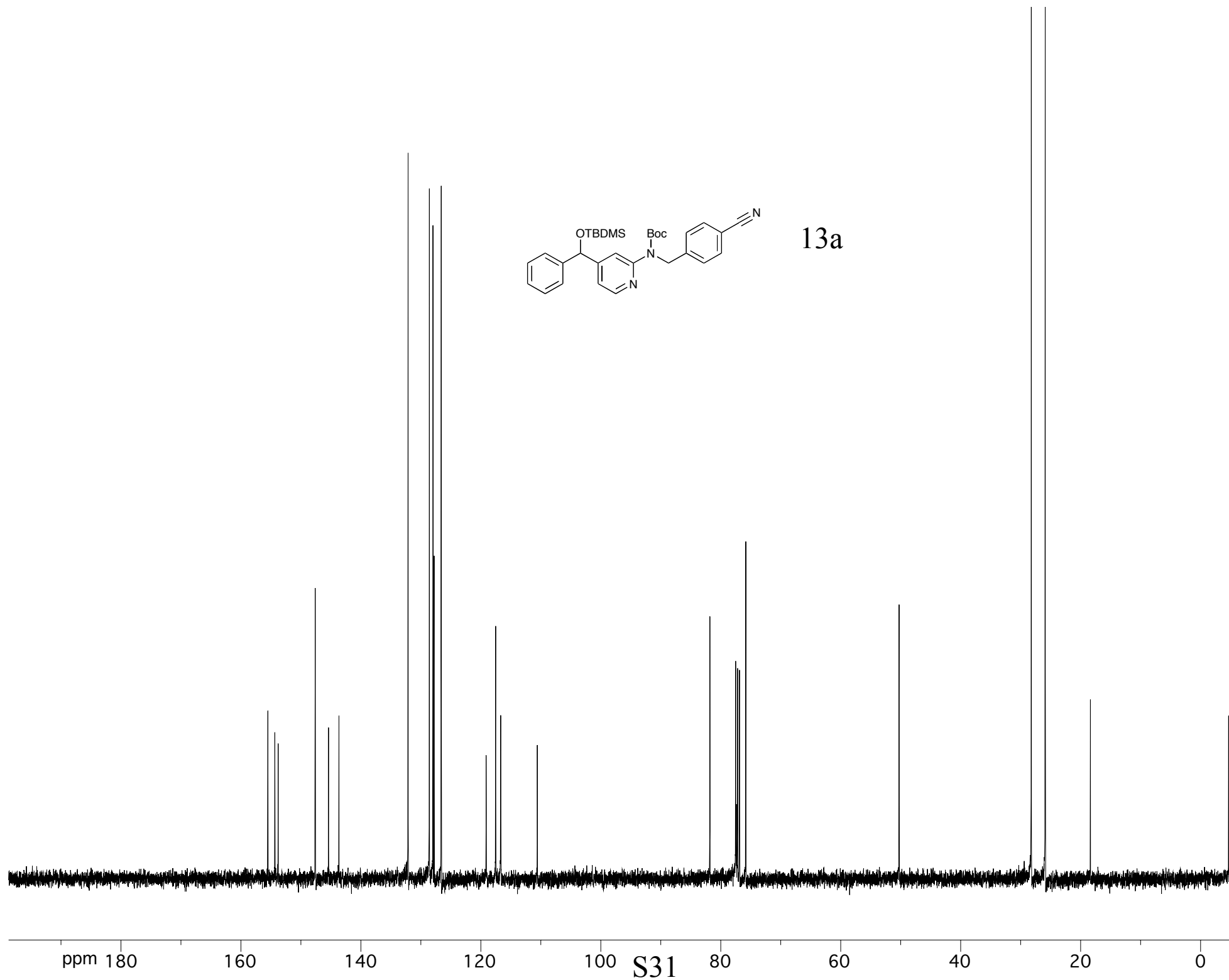


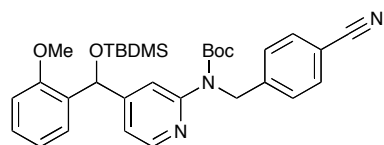
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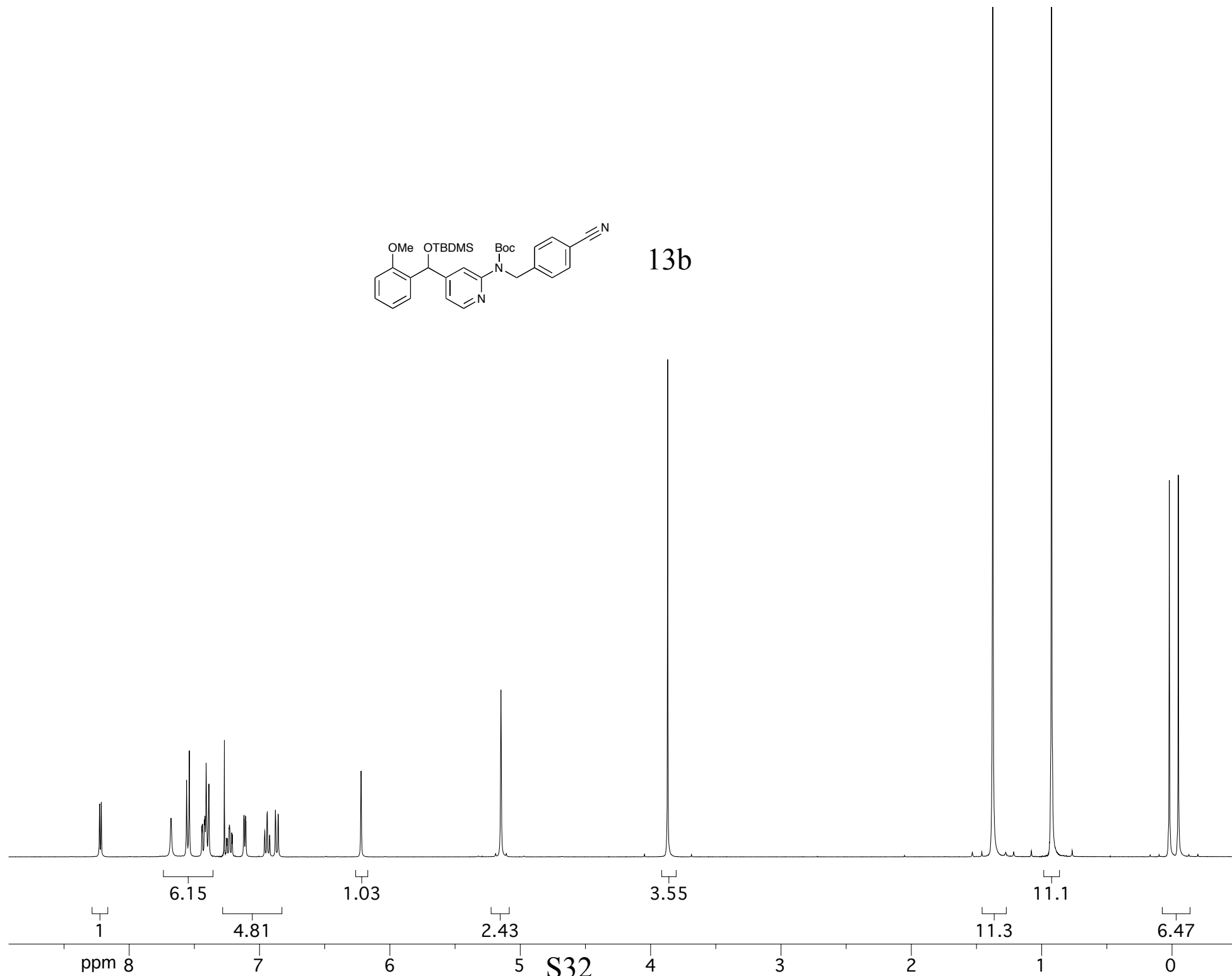


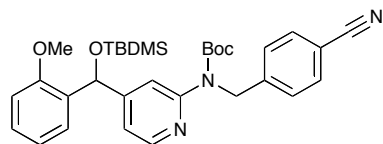
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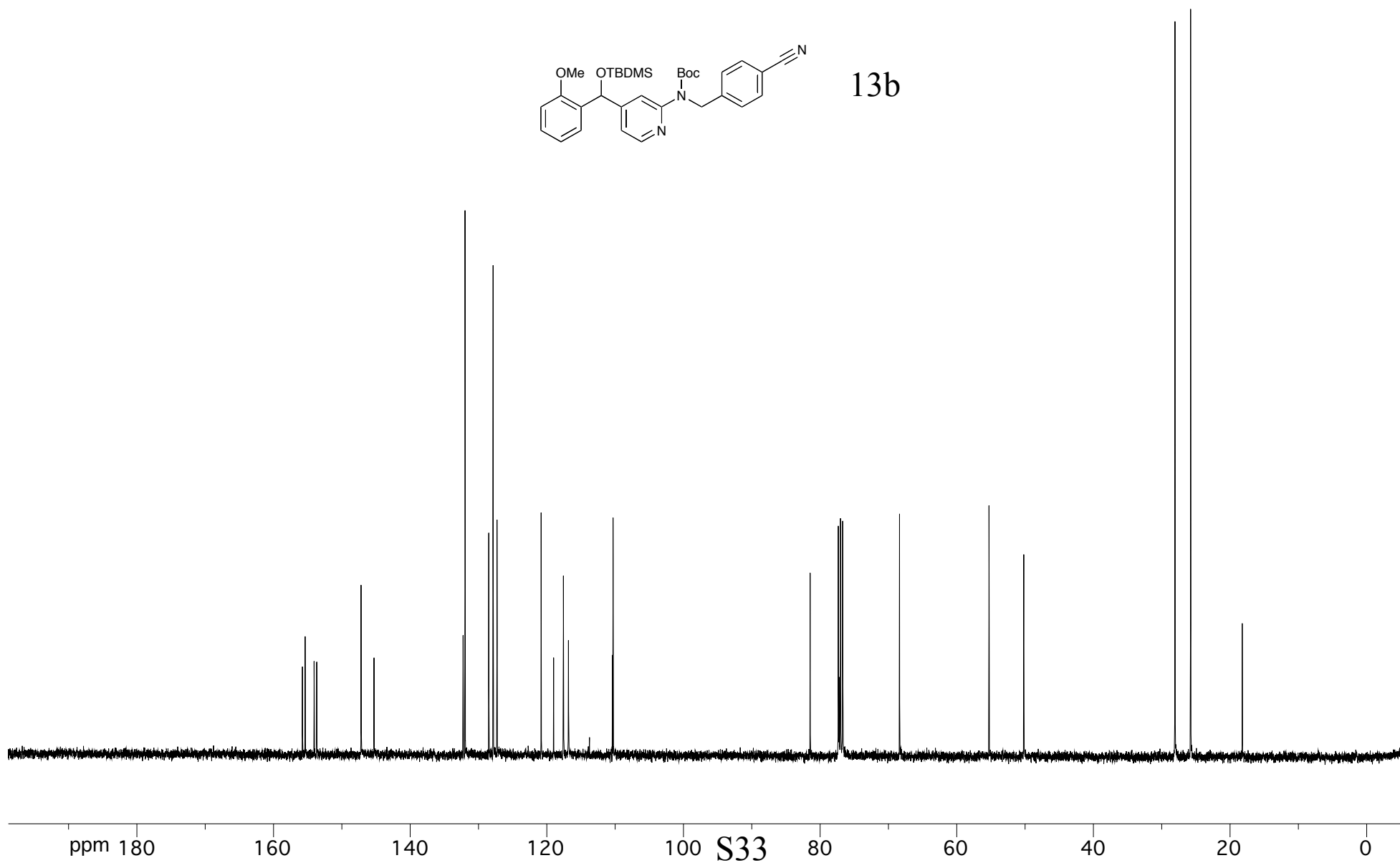


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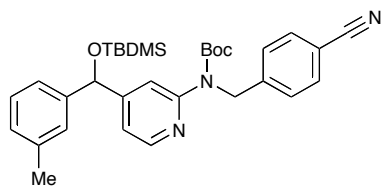




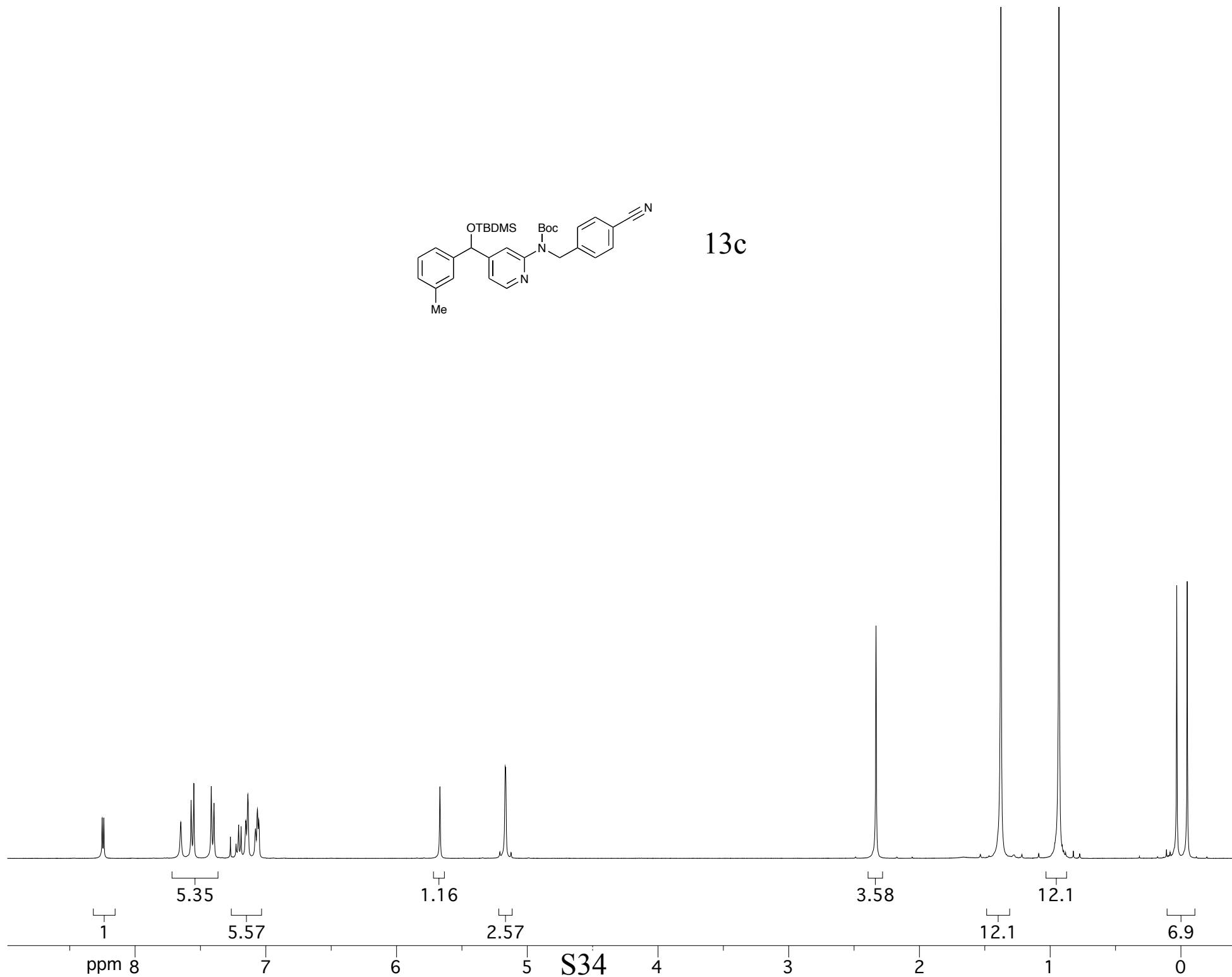
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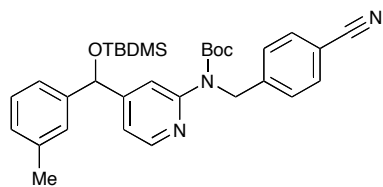


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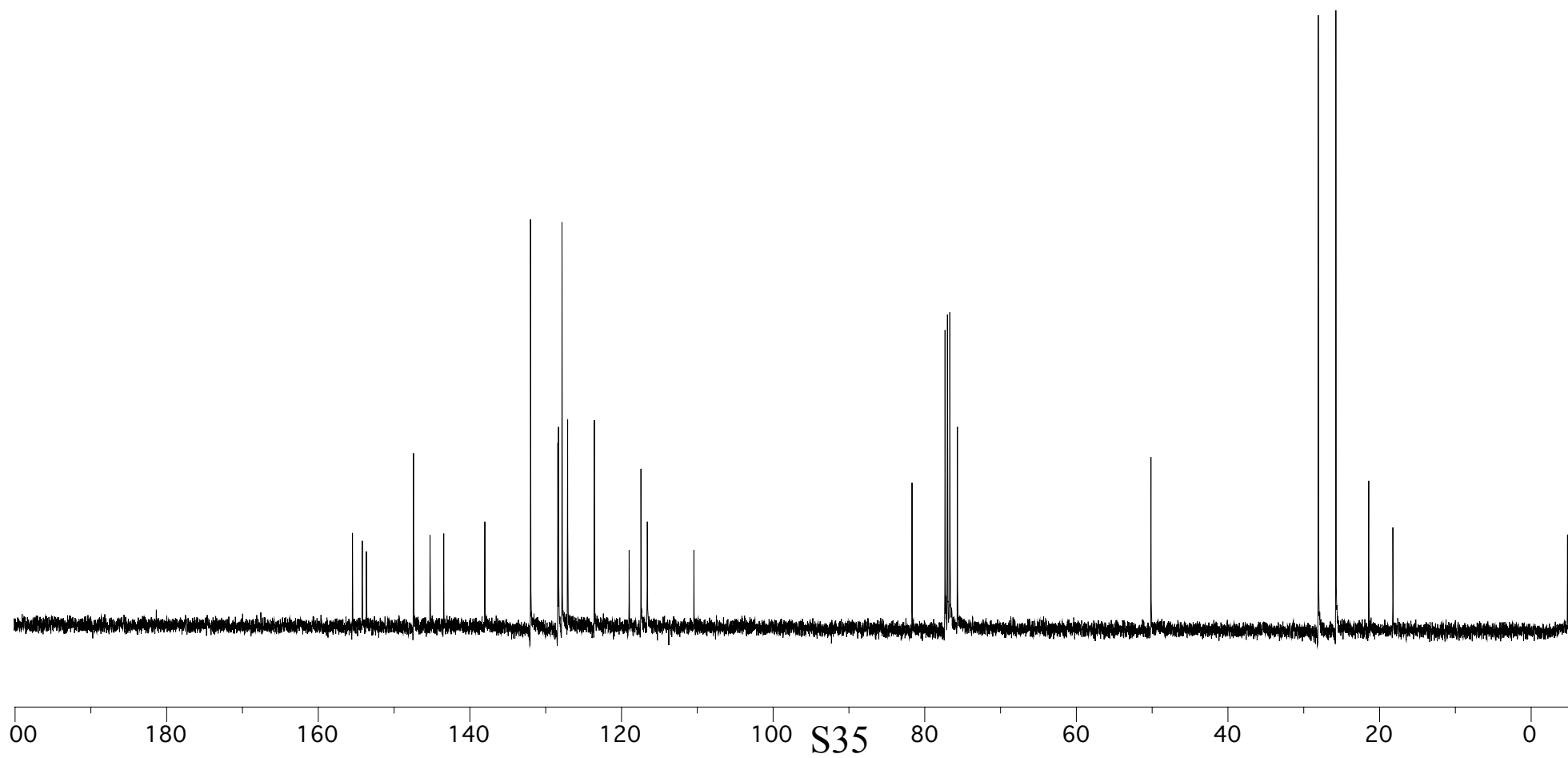


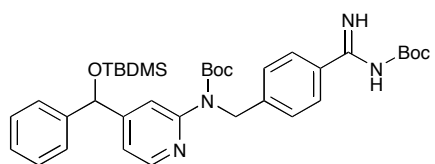
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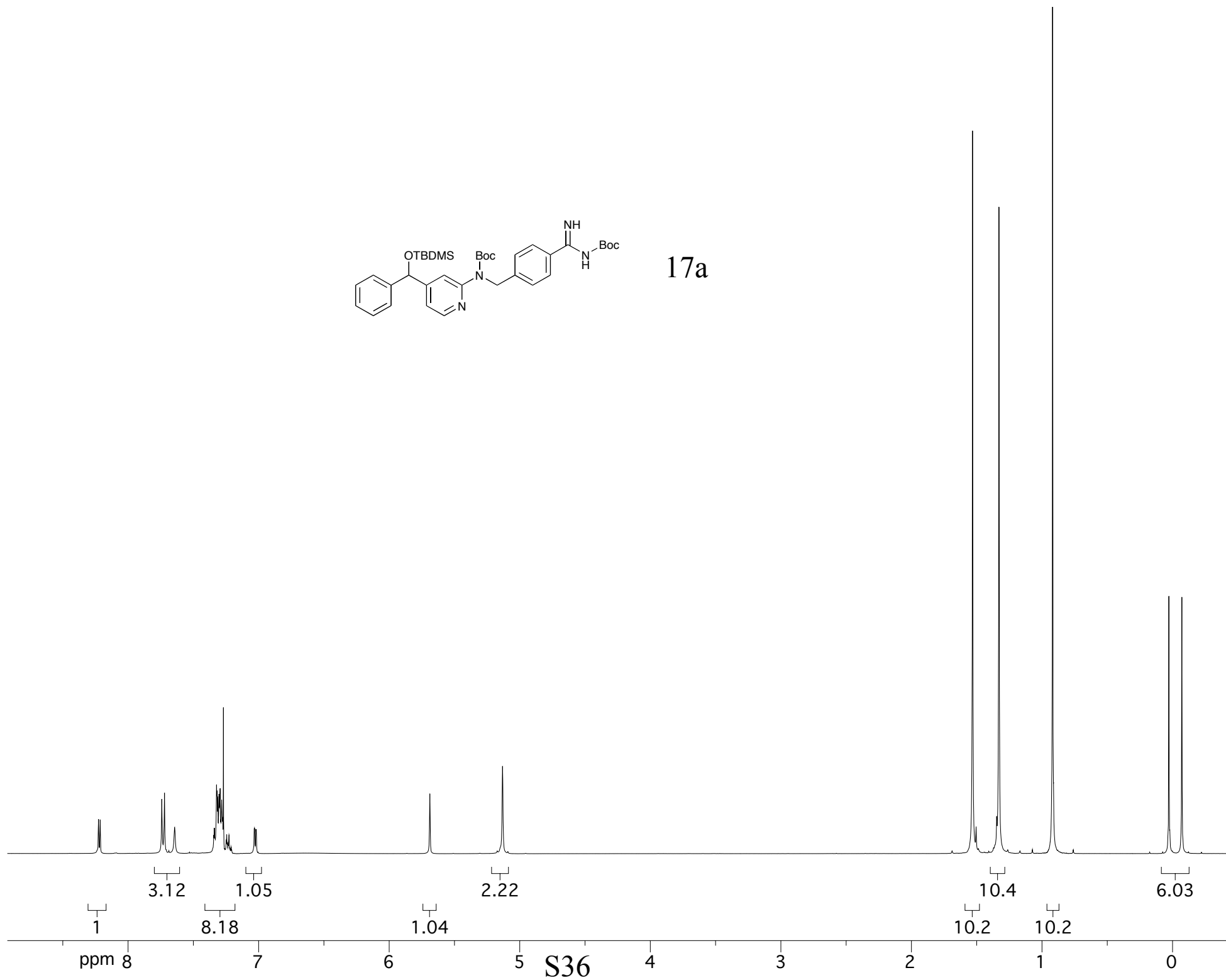


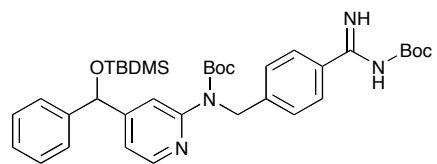
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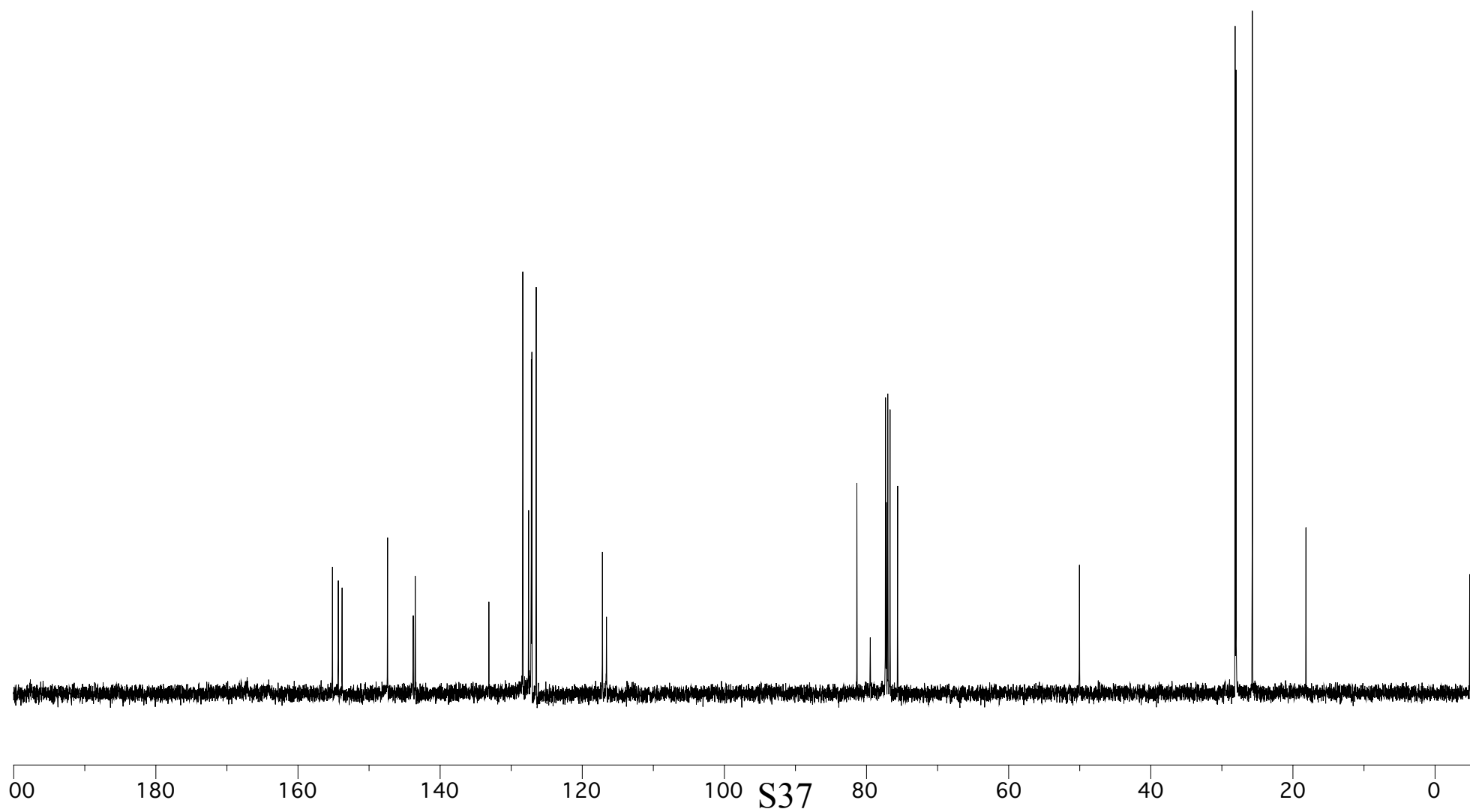


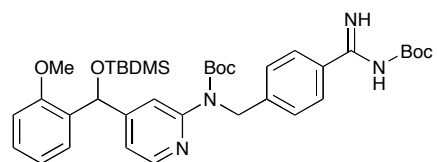
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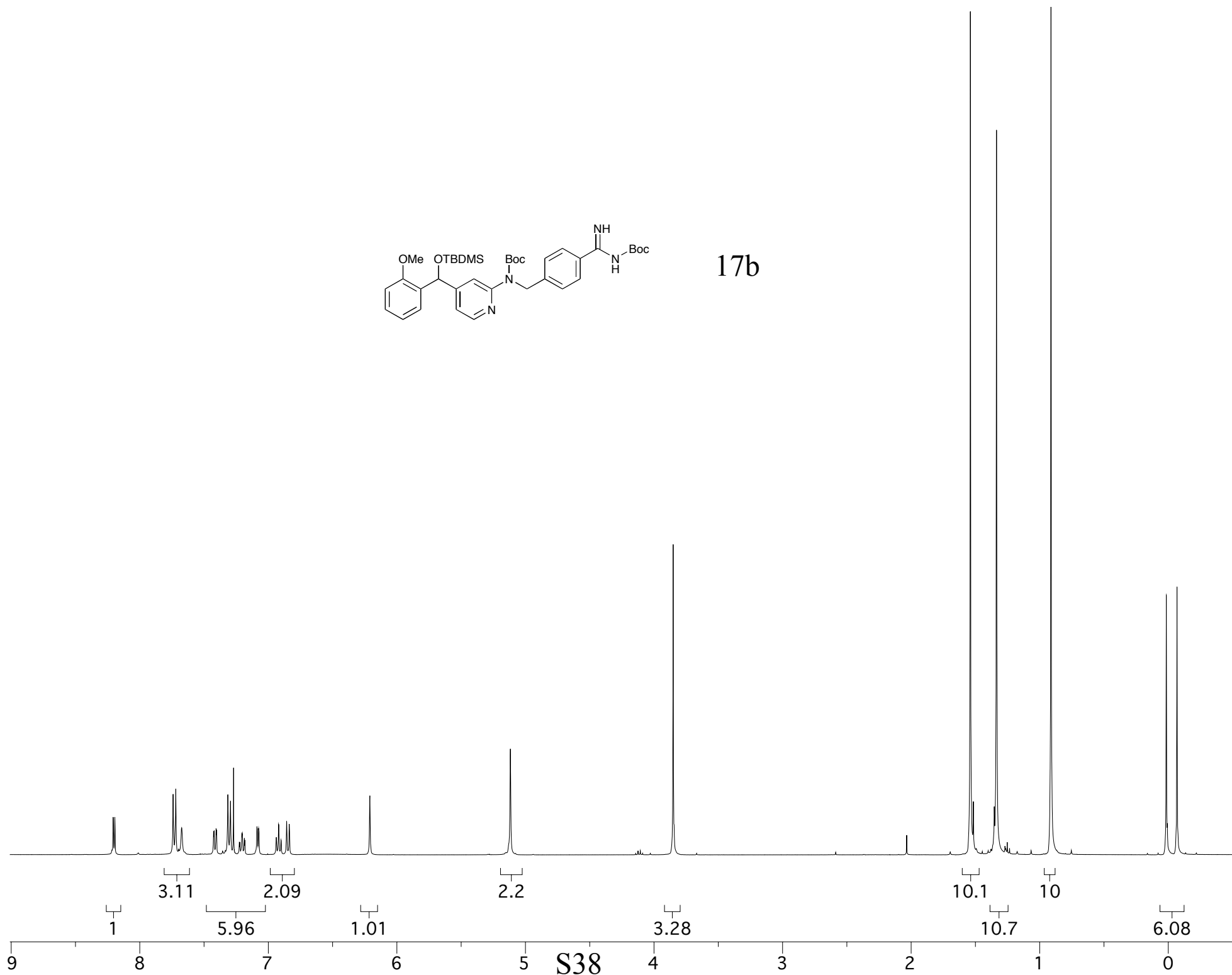


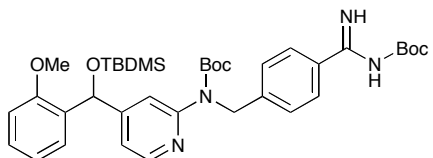
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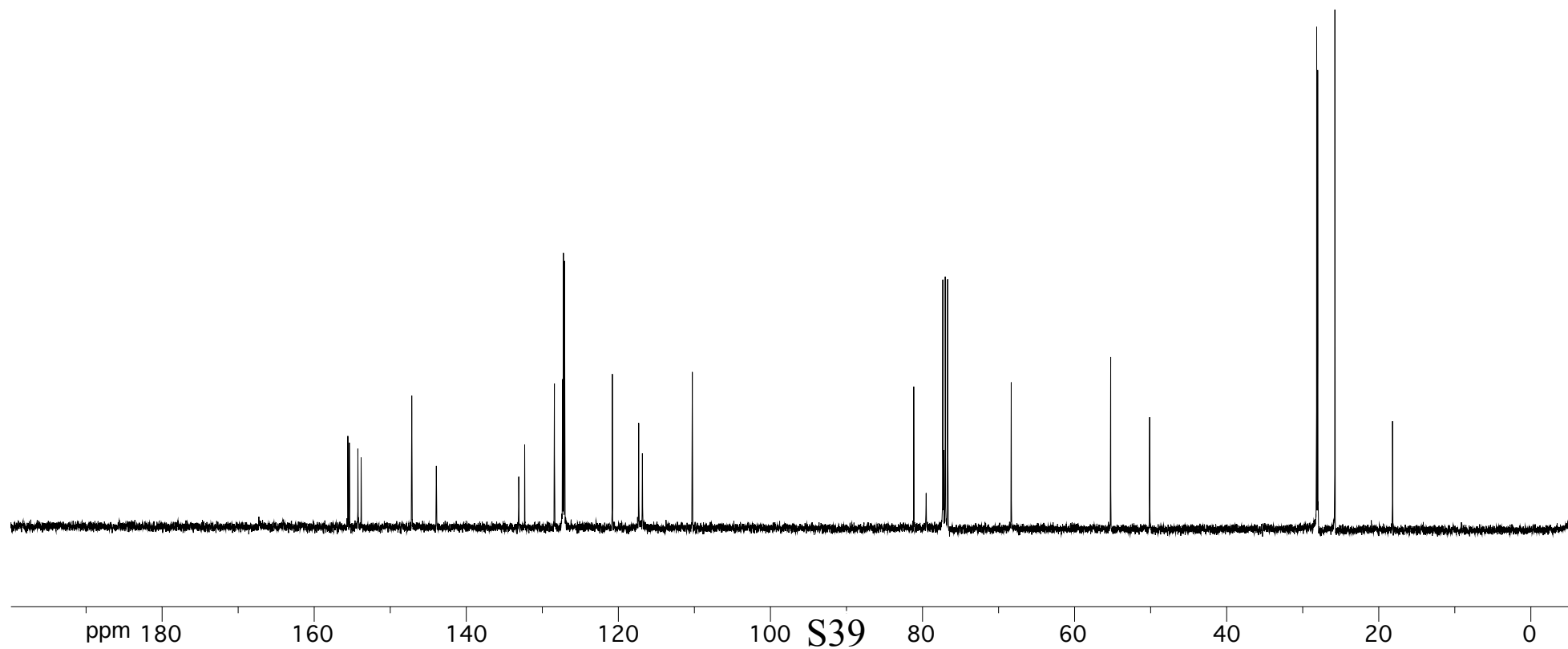


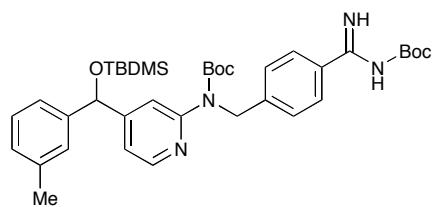
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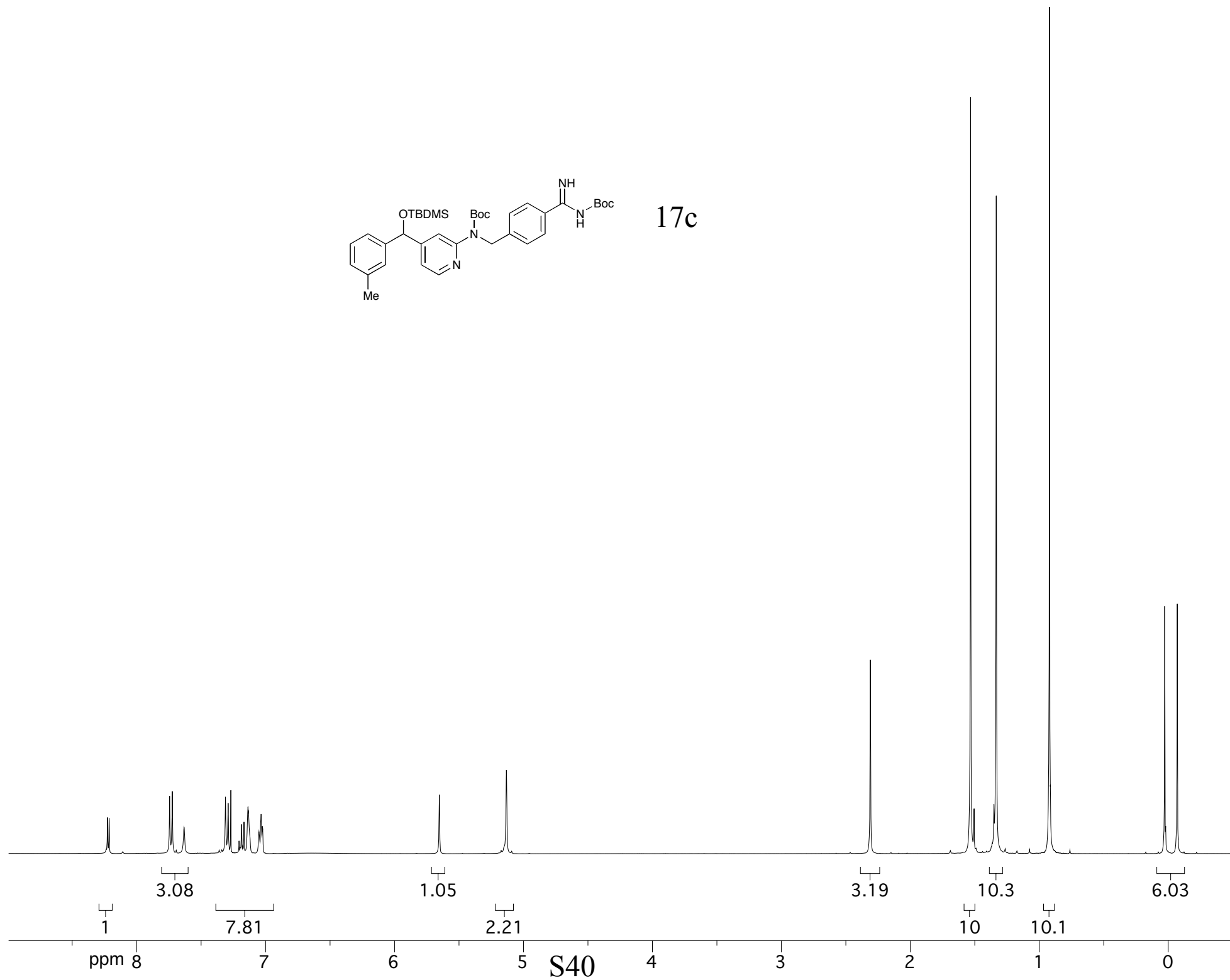


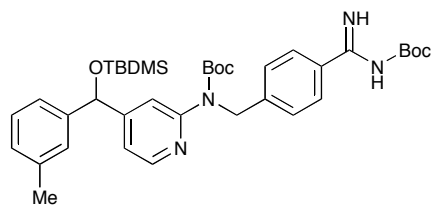
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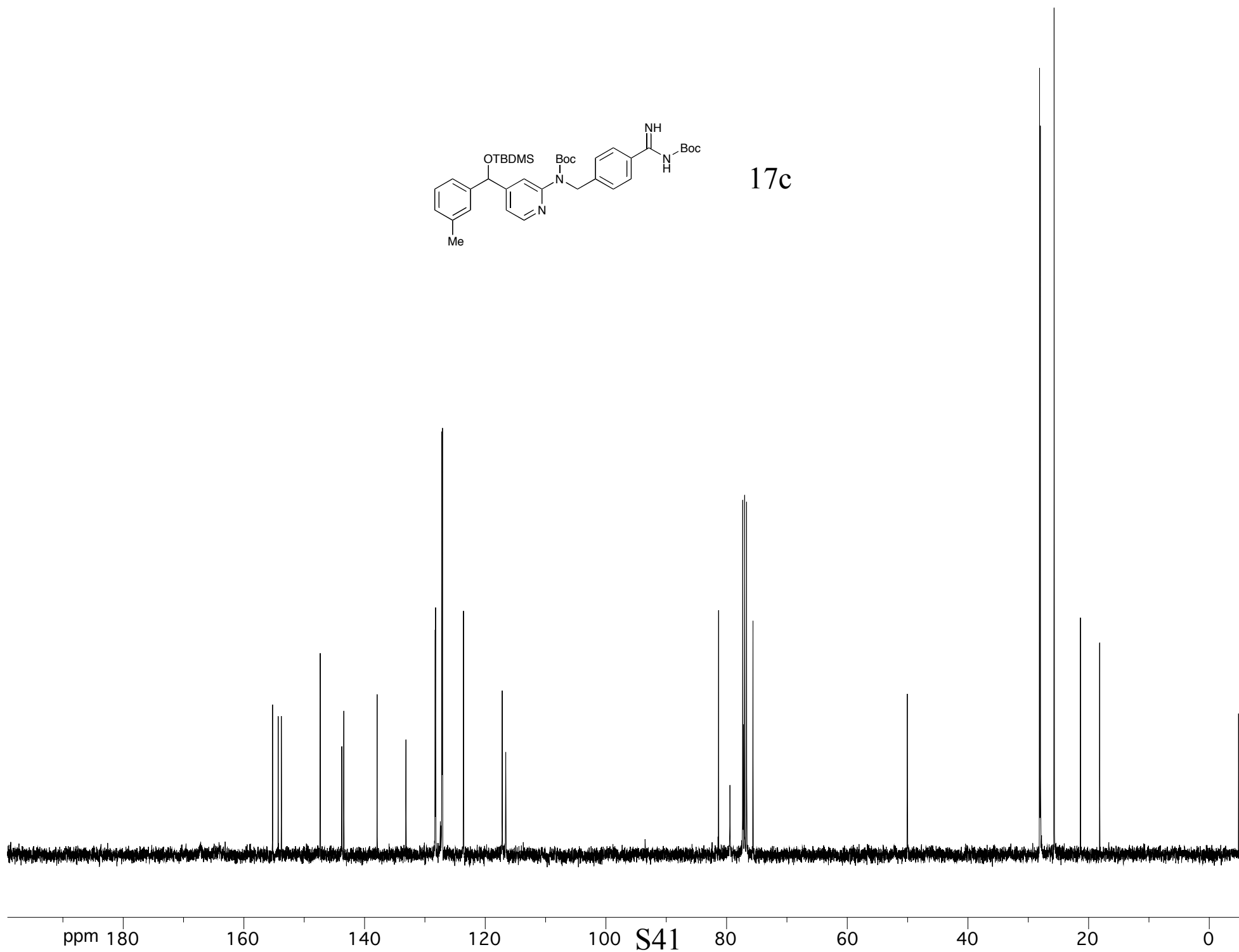


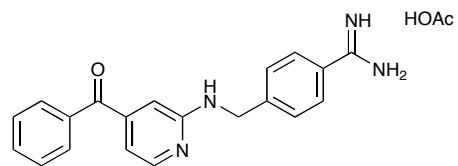
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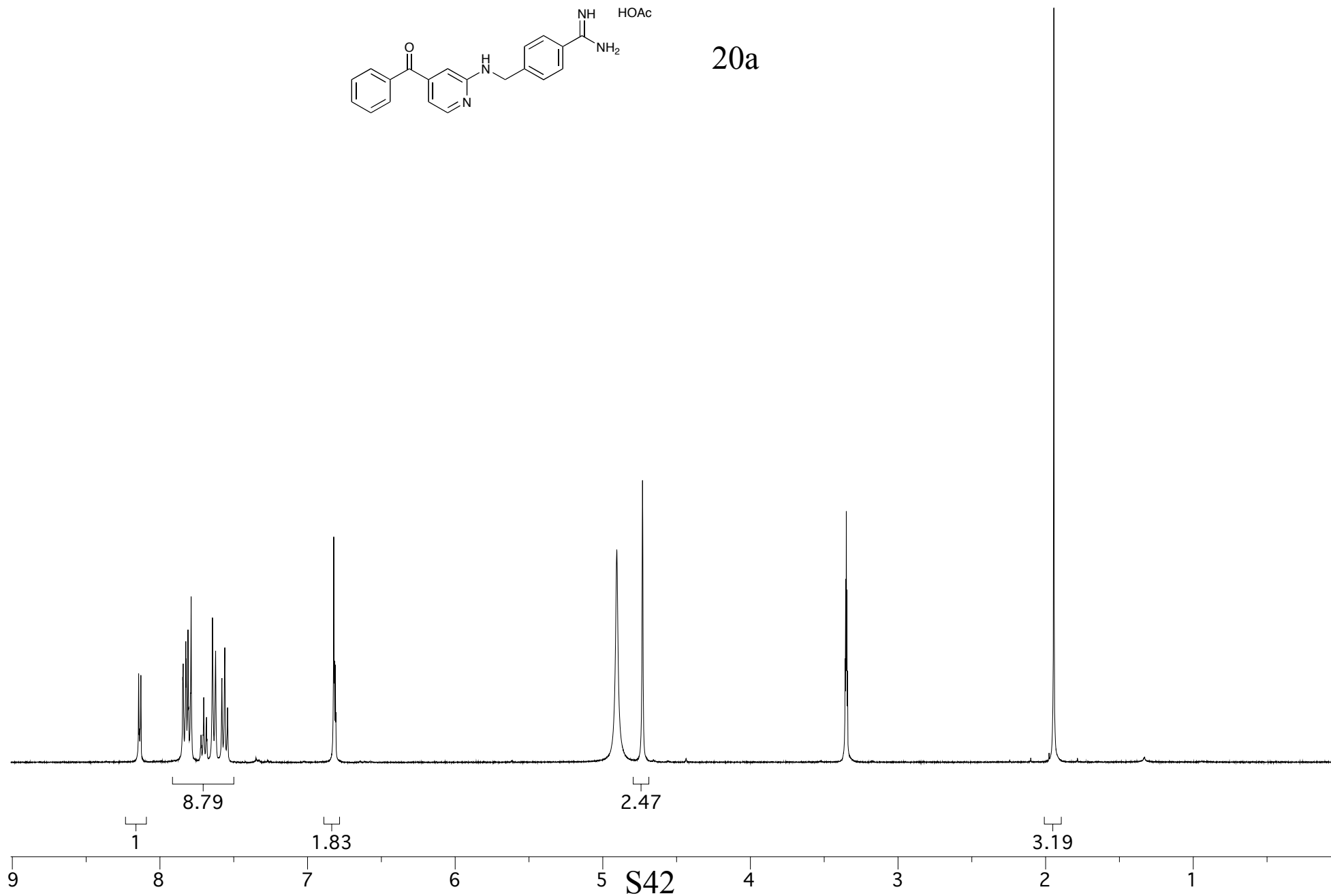


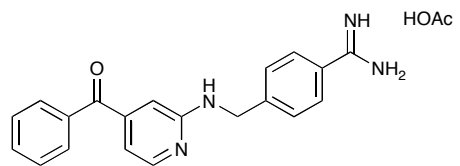
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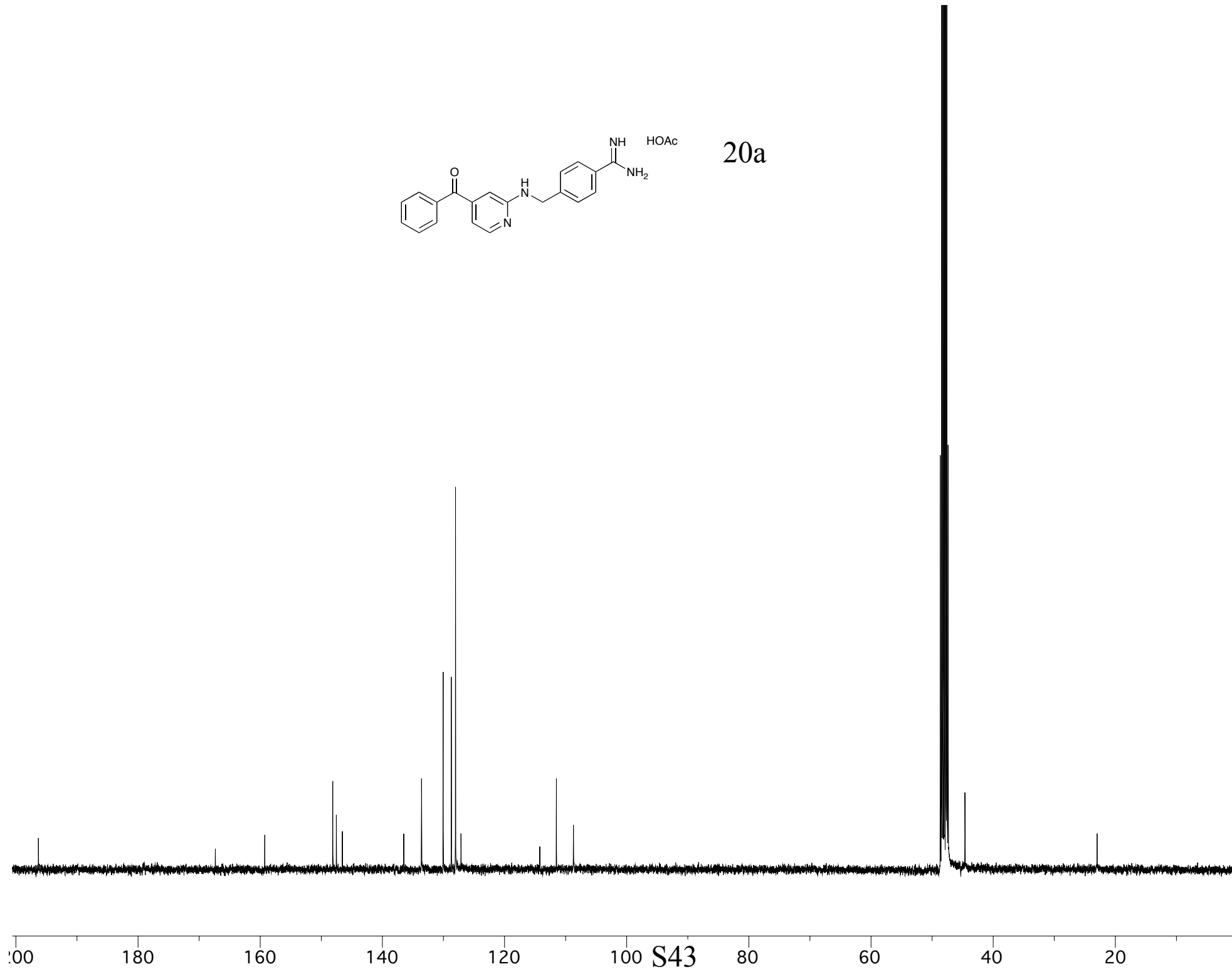


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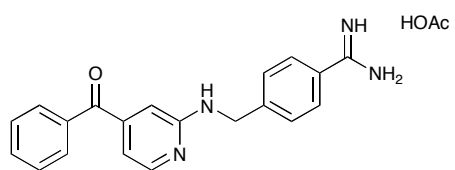




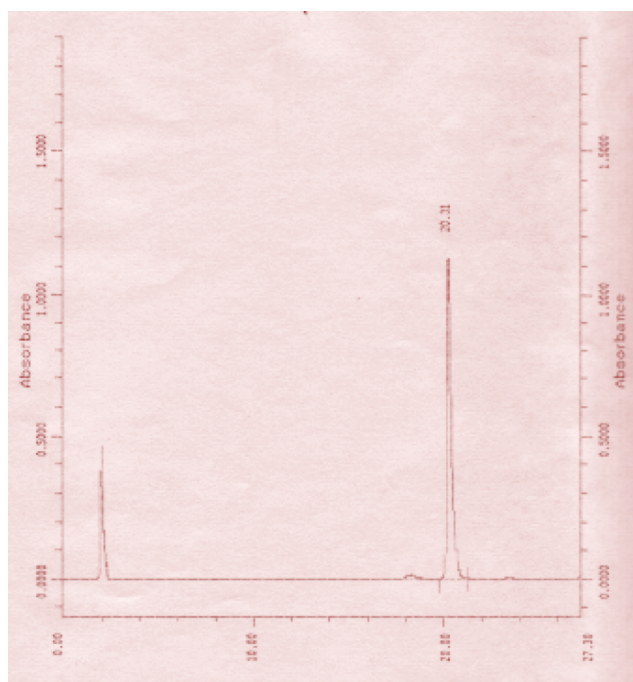
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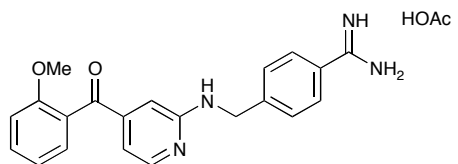


Chromatogram for compound.

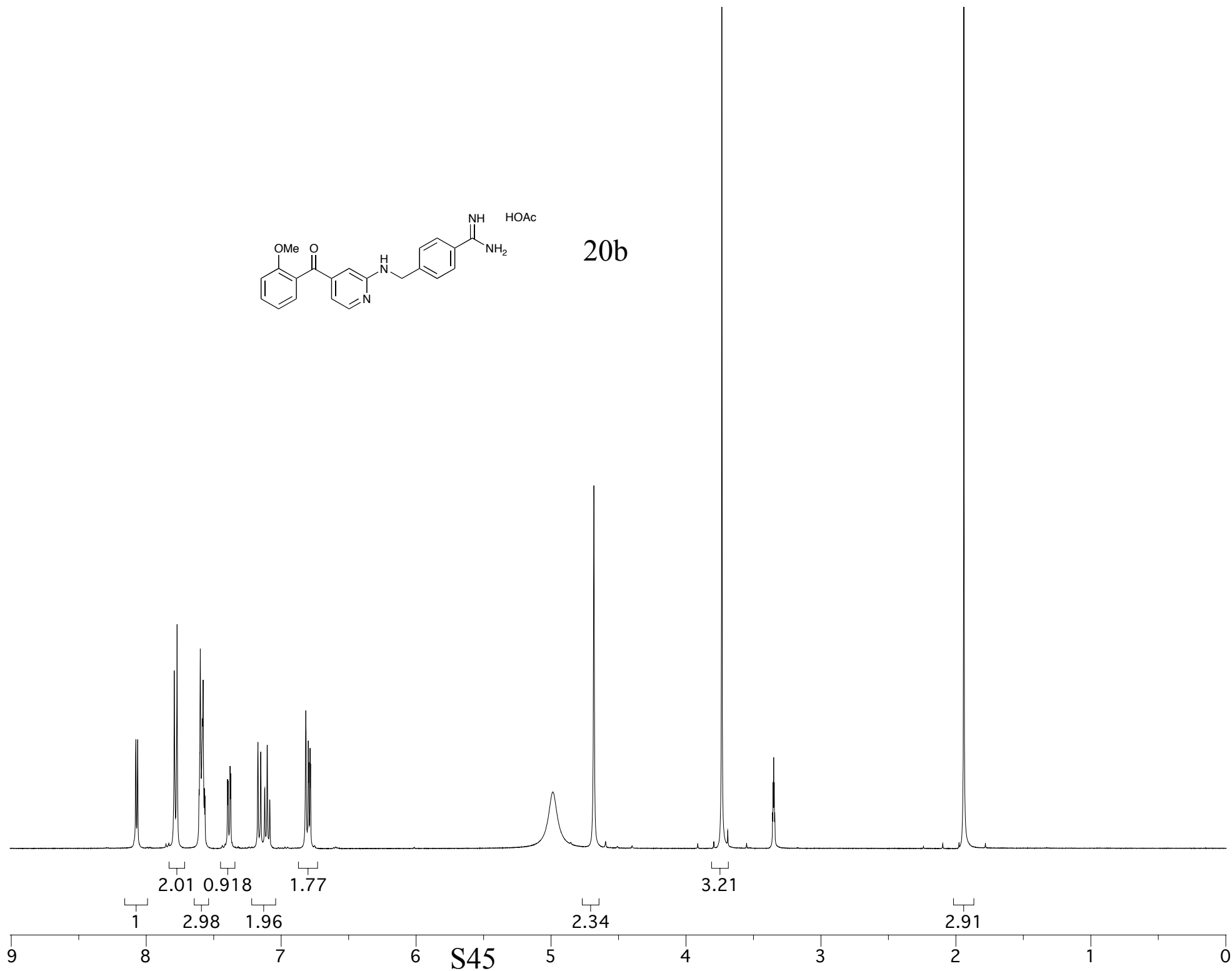


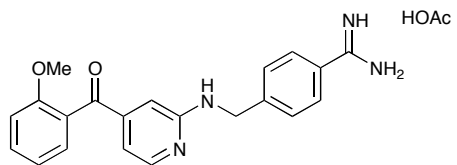
20a



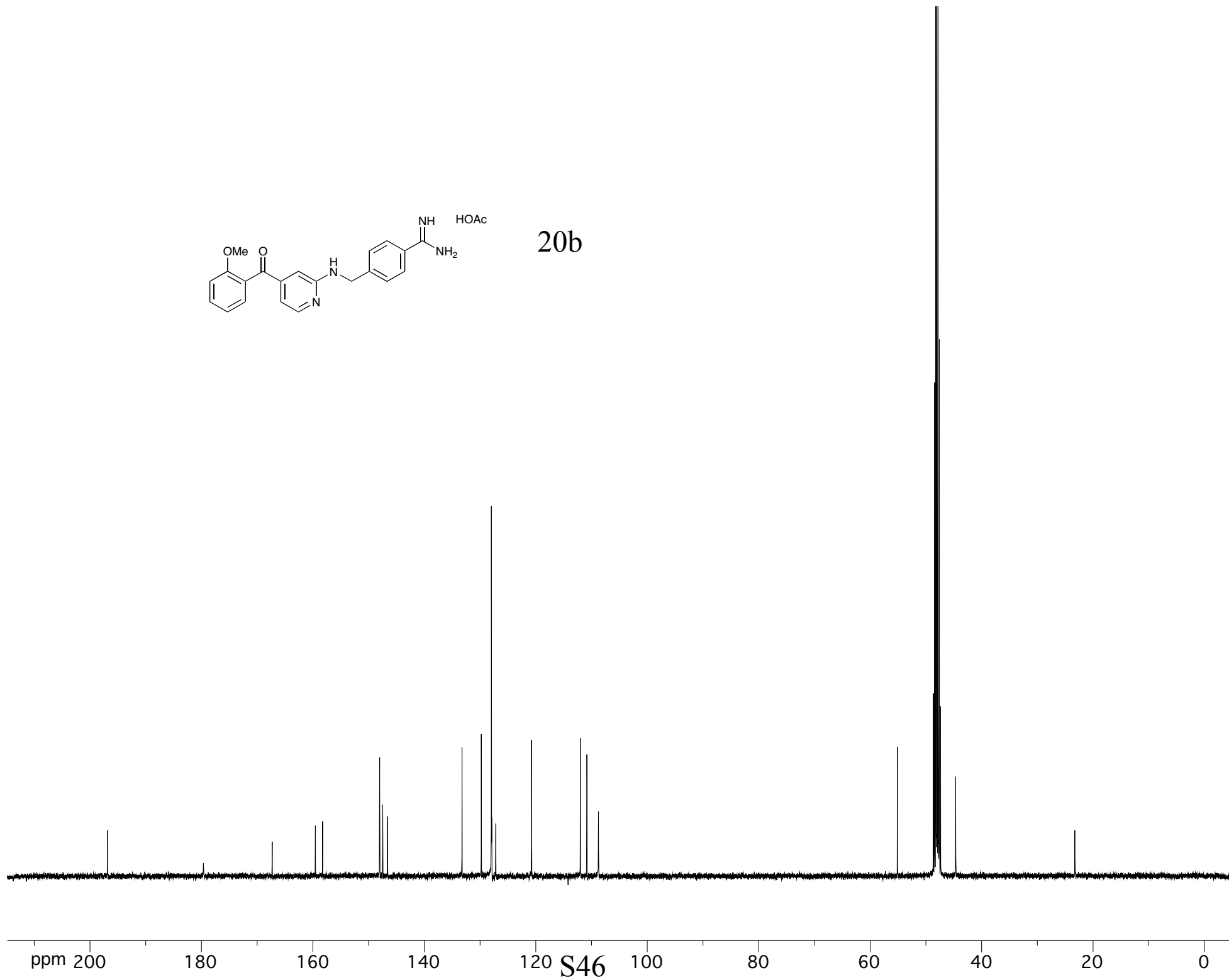


20b

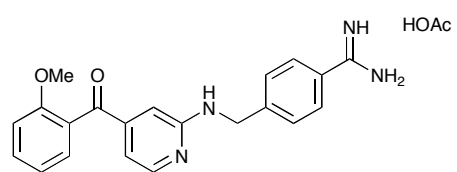




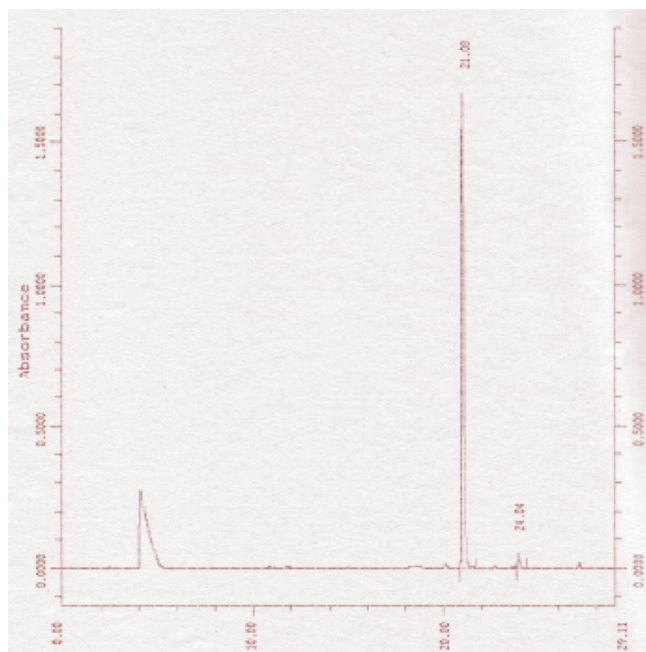
20b

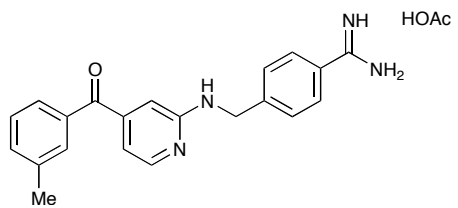


Chromatogram for compound.

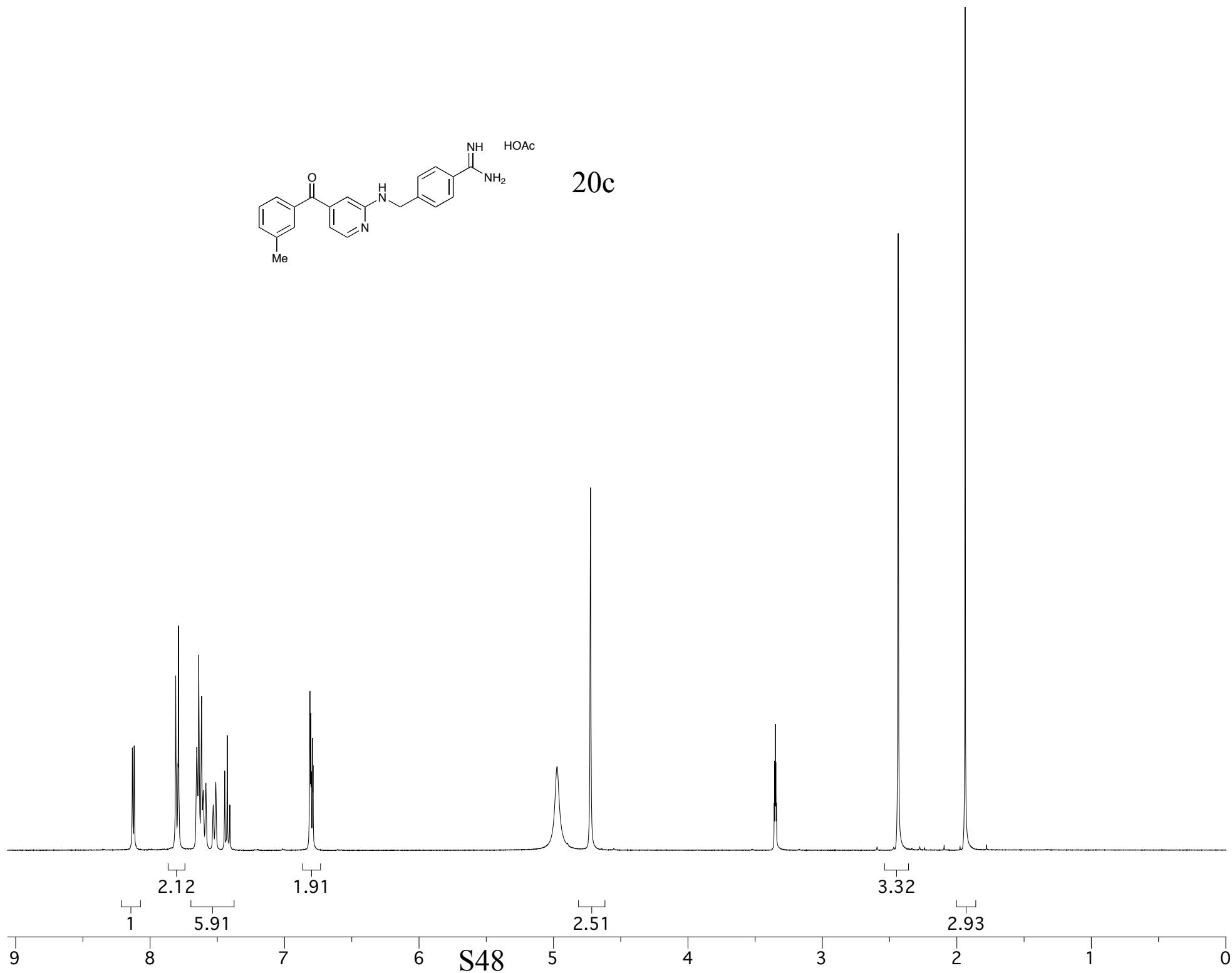


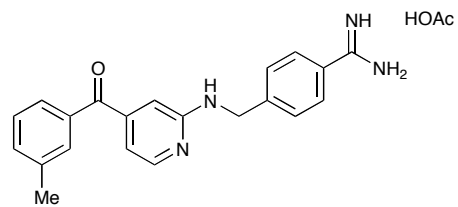
20b



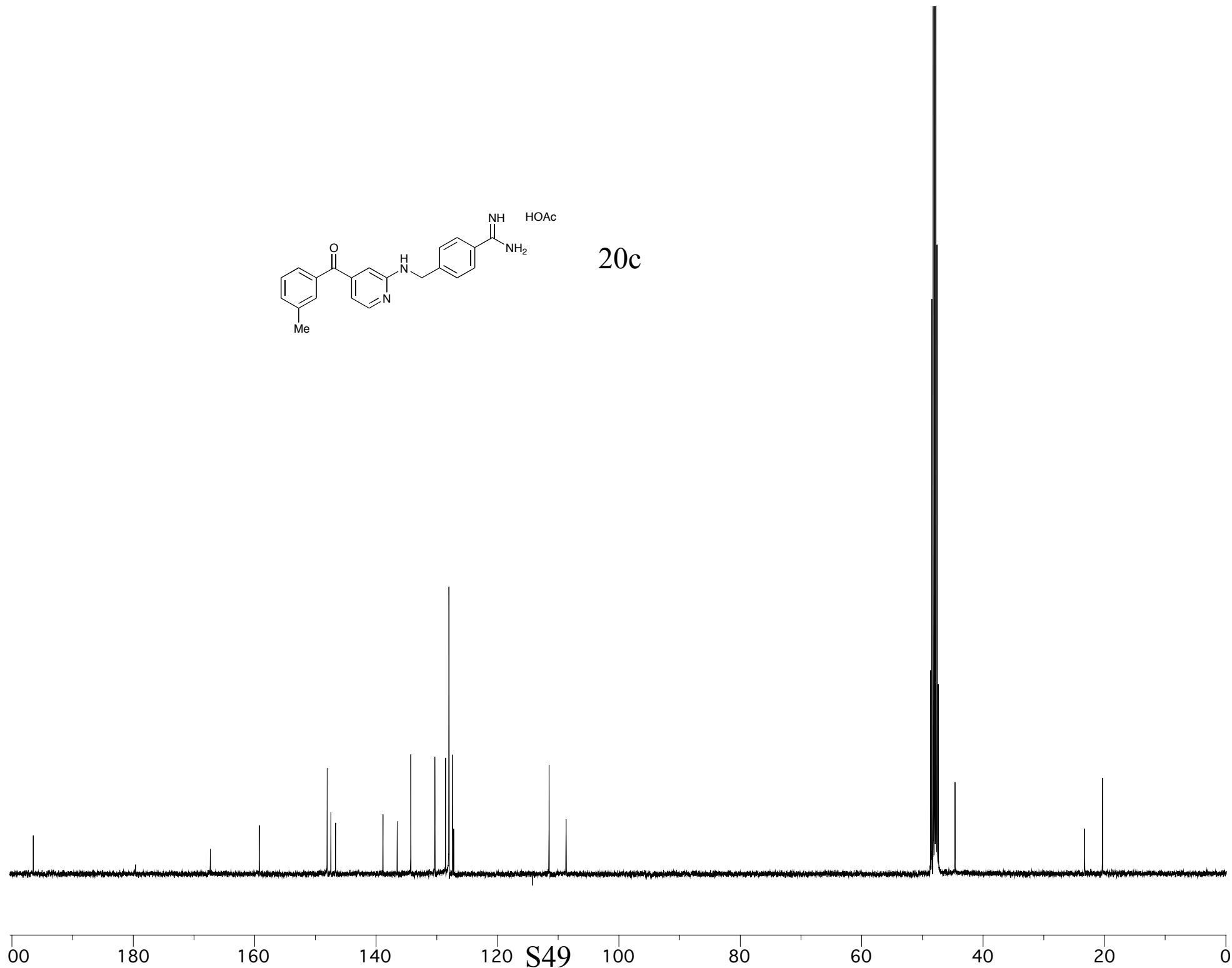


20c

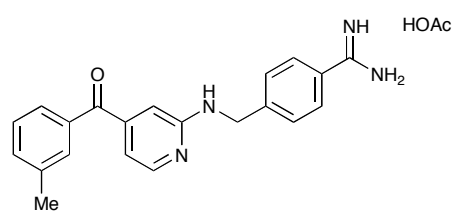




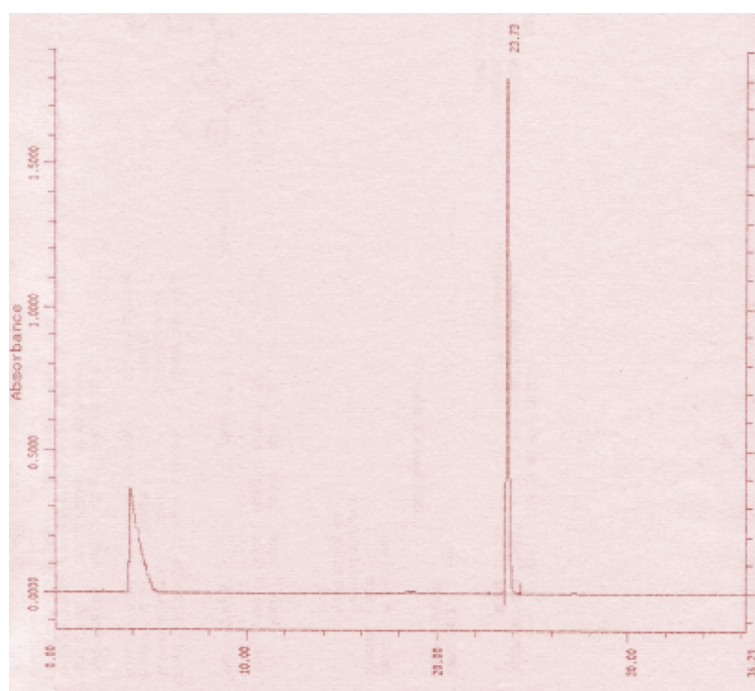
20c



Chromatogram for compound.



20c



Data collection and refinement statistics

	Parameters/value
Data collection	In house
Space group	C2
Cell dimensions	
a, b, c (Å)	69.9 71.8 70.8
α, β, γ (°)	90 100.2 90
Wavelength	1.5418
Resolution (Å)	69.7 – 2.5 (2.50-2.57) *
R_{sym} or R_{merge}	0.086 (0.423)
$I/\sigma I$	6.7 (1.8)
Completeness (%)	91.1 (93.9)
Redundancy	2.3 (2.2)
Refinement	
Resolution (Å)	2.50
No. reflections	10051
$R_{\text{work}}/R_{\text{free}}$	0.184/0.258
No. atoms	
Protein	2311
Ligand/ion	26
Water	47
B-factors	
Protein	41.8
Ligand/ion	36.8
Water	36.9
R.m.s deviations	
Bond lengths (Å)	0.019
Bond angles (°)	1.915

*Highest resolution shell is shown in parenthesis.

1. Leslie AG (1999) *Acta Crystallogr D* 55:1696–1702.
2. Collaborative Computational Project No 4 (1994) *Acta Crystallogr D* 50: 750–763.
3. Murshudov GN, Vagin AA, Lebedev A, Wilson KS, Dodson EJ (1999) *Acta Crystallogr D* 55:247–255.
4. Emsley P, Cowtan K (2004) *Acta Crystallographica Section D* 60: 2126-2132

Chemical shifts for all isolated compounds:

Compound 2a: ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 5.3$ Hz, 1H), 7.36-7.24 (m, 5H), 7.11 (d, $J = 5.3$ Hz, 1H), 6.99 (s, 1H), 5.75 (s, 1H), 3.98 (bs, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8 (d, $J_{\text{C-F}} = 239$ Hz), 159.1 (d, $J_{\text{C-F}} = 8$ Hz), 147.0 (d, $J_{\text{C-F}} = 14$ Hz), 142.1, 128.8, 128.3, 126.7, 119.1 (d, $J_{\text{C-F}} = 4$ Hz), 106.8 (d, $J_{\text{C-F}} = 38$ Hz), 74.4 (d, $J_{\text{C-F}} = 3$ Hz); HRMS (FAB) calcd for $\text{C}_{12}\text{H}_{11}\text{FNO}$ ($\text{M}+\text{H}$) 204.0825, found 204.0818.

Compound 2b: No data recorded.

Compound 2c: ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 5.3$ Hz, 1H), 7.28-7.21 (m, 1H), 7.16-7.09 (m, 4H), 7.02 (s, 1H), 5.74 (s, 1H), 3.32 (bs, 1H), 2.34 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0 (d, $J_{\text{C-F}} = 240$ Hz), 159.0 (d, $J_{\text{C-F}} = 7.5$ Hz), 147.2 (d, $J_{\text{C-F}} = 14$ Hz), 142.1, 138.7, 129.3, 128.8, 127.5, 123.9, 119.1 (d, $J_{\text{C-F}} = 3.9$ Hz), 106.8 (d, $J_{\text{C-F}} = 38$ Hz), 74.6 (d, $J_{\text{C-F}} = 2.9$ Hz), 21.3.

Compound 3a: ^1H NMR (400 MHz, CDCl_3) δ 8.33-8.29 (m, 1H), 7.76-7.72 (m, 2H), 7.61-7.56 (m, 1H), 7.47-7.42 (m, 2H), 7.40 (ddd, $J = 5.1$, 2.1 and 1.3 Hz, 1H), 7.14-7.12 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.2 (d, $J_{\text{C-F}} = 3$ Hz), 163.6 (d, $J_{\text{C-F}} = 240$ Hz), 149.8 (d, $J_{\text{C-F}} = 7$ Hz), 148.2 (d, $J_{\text{C-F}} = 15$ Hz), 135.2, 133.7, 129.9, 128.6, 120.6 (d, $J_{\text{C-F}} = 4$ Hz), 109.2 (d, $J_{\text{C-F}} = 39$ Hz); HRMS (FAB) calcd for $\text{C}_{12}\text{H}_9\text{FNO}$ ($\text{M}+\text{H}$) 202.0668, found 202.0663.

Compound 3b: ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 5.1$ Hz, 1H), 7.58-7.42 (m, 3H), 7.20-7.16 (m, 1H), 7.11-7.06 (m, 1H), 7.02-6.98 (m, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.8 (d, $J_{\text{C-F}} = 3.1$ Hz), 164.2 (d, $J_{\text{C-F}} = 240$ Hz), 157.9, 150.5 (d, $J_{\text{C-F}} = 7.0$ Hz), 148.1 (d, $J_{\text{C-F}} = 15$ Hz), 133.8, 130.4, 126.7, 121.0, 120.1 (d, $J_{\text{C-F}} = 4.8$ Hz), 111.6, 108.8 (d, $J_{\text{C-F}} = 39$ Hz), 55.4; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{11}\text{FNO}_2$ ($\text{M}+\text{H}$) 232.0774, found 232.0777.

Compound 3c: ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, $J = 5.1$ Hz, 1H), 7.64-7.60 (m, 1H), 7.58-7.53 (m, 1H), 7.48-7.42 (m, 2H), 7.41-7.34 (m, 1H), 7.19-7.15 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.5 (d, $J_{\text{C-F}} = 3.0$ Hz), 163.7 (d, $J_{\text{C-F}} = 240$ Hz), 150.1 (d, $J_{\text{C-F}} = 6.8$ Hz), 148.2 (d, $J_{\text{C-F}} = 15$ Hz), 138.7, 135.4, 134.6, 130.3, 128.5, 127.3, 120.6 (d, $J_{\text{C-F}} = 4.6$ Hz), 109.3 (d, $J_{\text{C-F}} = 39$ Hz), 21.2; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{11}\text{FNO}$ ($\text{M}+\text{H}$) 216.0825, found 216.0819.

Compound 6a: ^1H NMR (400 MHz, CDCl_3) contains heptane δ 8.19 (dd, $J = 5.2$ and 0.7 Hz, 1H), 7.81 (dd, $J = 7.1$ and 1.4 Hz, 2H), 7.65-7.57 (m, 1H), 7.48 (t, $J = 7.1$ Hz, 2H), 6.87 (dd, $J = 3.8$ and 1.4 Hz, 1H), 6.75 (dd, $J = 1.4$ and 0.7 Hz, 1H), 4.75 (br s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.7, 158.8, 148.6, 146.5, 136.1, 133.3, 130.1, 128.5, 113.2, 108.0; HRMS (FAB) calcd for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) 199.0871, found 199.0876.

Compound 6b: ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, $J = 5.3$ Hz, 1H), 7.53-7.38 (m, 2H), 7.07-6.96 (m, 2H), 6.87 (dd, $J = 5.3$ and 1.3 Hz, 1H), 6.80 (s, 1H), 4.68 (bs, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.7, 158.9, 157.8, 148.4, 146.8, 132.9, 130.1, 127.6, 120.6, 112.9, 111.6, 107.8, 55.6; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) 229.0977, found 229.0973.

Compound 6c: ^1H NMR (400 MHz, CDCl_3) δ 8.15 (dd, $J = 5.2$ and 0.6 Hz, 1H), 7.63-7.53 (m, 2H), 7.40-7.29 (m, 2H), 6.81 (dd, $J = 5.2$ and 1.4 Hz, 1H), 6.73-6.72 (m, 1H), 5.00 (bs, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 158.9, 148.3, 146.5, 138.3, 136.0, 134.0, 130.3, 128.1, 127.3, 112.8, 108.0, 21.1; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) 213.1028, found 213.1027.

Compound 8a: ^1H NMR (400 MHz, CDCl_3) δ 8.47 (dd, $J = 5.0$ and 0.7 Hz, 1H), 8.09 (s, 1H), 7.87-7.83 (m, 2H), 7.68-7.40 (m, 7H), 7.26 (dd, $J = 5.0$ and 1.3 Hz, 1H), 5.26 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.9, 154.6, 153.5, 147.8, 146.1, 145.0, 135.8, 133.5, 132.1, 130.2, 128.6, 127.7, 118.9, 118.6, 118.1, 110.6, 82.4, 49.8, 28.0; HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$) 414.1818, found 414.1825.

Compound 8b: ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 5.1$ Hz, 1H), 8.04 (s, 1H), 7.60-7.39 (m, 6H), 7.24 (dd, $J = 5.1$ and 1.3 Hz, 1H), 7.05 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 5.24 (s, 2H), 3.68 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.0, 157.8, 154.7, 153.4, 147.7, 146.1, 145.0, 133.2, 132.0, 130.2, 127.7, 127.1, 120.7, 118.8, 118.2, 117.9, 111.5, 110.5, 82.1, 55.4, 49.7, 27.9; HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$) 444.1923, found 444.1946.

Compound 8c: ^1H NMR (400 MHz, CDCl_3) δ 8.47 (d, $J = 5.1$ Hz, 1H), 8.09 (s, 1H), 7.70 (s, 1H), 7.65-7.58 (m, 3H), 7.47-7.37 (m, 3H), 7.28-7.26 (m, 2H), 5.27 (s, 2H), 2.43 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.0, 154.6, 153.6, 147.8,

146.2, 145.0, 138.6, 135.8, 134.3, 132.1, 130.6, 128.4, 127.7, 127.5, 118.9, 118.6, 118.2, 110.6, 82.4, 49.8, 28.0, 21.3; HRMS (FAB) calcd for $C_{26}H_{26}N_3O_3$ (M+H) 428.1974, found 428.1992.

Compound 13a: 1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, $J = 5.2$ Hz, 1H), 7.68 (s, 1H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.37-7.29 (m, 4H), 7.28-7.24 (m, 1H), 7.06 (dd, $J = 5.2$ and 1.0 Hz, 1H), 5.71 (s, 1H), 5.17 (s, 2H), 1.38 (s, 9H), 0.94 (s, 9H), 0.04 (s, 3H), - 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.2, 153.6, 147.4, 145.2, 143.5, 132.0, 128.4, 127.8, 127.7, 126.5, 119.0, 117.4, 116.5, 110.4, 81.7, 75.7, 50.2, 28.1, 25.7, 18.2, - 4.9, - 5.0; HRMS (FAB) calcd for $C_{31}H_{40}N_3O_3Si$ (M+H) 530.2839, found 530.2829.

Compound 13b: 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 5.2$ Hz, 1H), 7.68 (s, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.43 (dd, $J = 7.8$ and 1.7 Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.26-7.20 (m, 1H), 7.13-7.10 (m, 1H), 6.97-6.92 (m, 1H), 6.87 (d, $J = 8.3$ Hz, 1H), 6.22 (s, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 1.38 (s, 9H), 0.93 (s, 9H), 0.02 (s, 3H), - 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 154.1, 153.7, 147.2, 145.3, 132.3, 132.0, 128.5, 127.9, 127.3, 120.8, 119.0, 117.6, 116.8, 110.4, 110.3, 81.5, 68.4, 55.3, 50.2, 28.1, 25.8, 18.2, - 5.0, - 5.1; HRMS (FAB) calcd for $C_{32}H_{42}N_3O_4Si$ (M+H) 560.2945, found 560.2941.

Compound 13c: 1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, $J = 5.2$ Hz, 1H), 7.65 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.24-7.12 (m, 3H), 7.09-7.04 (m, 2H), 5.67 (s, 1H), 5.17 (s, 2H), 2.34 (s, 3H), 1.38 (s, 9H), 0.93 (s, 9H), 0.03 (s, 3H) -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.2, 153.6, 147.4, 145.3, 143.5, 138.1, 132.0, 128.4, 128.3, 127.8, 127.1, 123.6, 119.0, 117.4, 116.6, 110.4, 81.7, 75.7, 50.1, 28.1, 25.7, 21.4, 18.2, -4.8, -5.0; HRMS (FAB) calcd for $C_{32}H_{42}N_3O_3Si$ (M+H) 544.2995, found 544.2993.

Compound 17a: 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 5.2$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.64 (s, 1H), 7.36-7.20 (m, 7H), 7.02 (dd, $J = 5.2$ and 1.1 Hz, 1H), 5.69 (s, 1H), 5.13 (s, 2H), 1.53 (s, 9H), 1.33 (s, 9H), 0.92 (s, 9H), 0.03 (s, 3H), - 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.3, 153.8, 147.4, 143.8, 143.5, 133.1, 128.4, 127.5, 127.2, 127.1, 126.5, 117.1, 116.6, 81.3, 79.5, 75.6, 50.0, 28.1, 28.0,

25.7, 18.2, - 4.9, - 5.0; HRMS (FAB) calcd for C₃₆H₅₁N₄O₅Si (M+H) 647.3629, found 647.3651.

Compound 17b: ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 5.2 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.67 (s, 1H), 7.41 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.23-7.18 (m, 1H), 7.08 (dd, *J* = 5.2 and 0.9 Hz, 1H), 6.94-6.90 (m, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.21 (s, 1H), 5.12 (s, 2H), 3.85 (s, 3H), 1.54 (s, 9H), 1.34 (s, 9H), 0.91 (s, 9H), 0.02 (s, 3H), - 0.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.6, 155.4, 154.3, 153.8, 147.2, 143.9, 133.1, 132.3, 128.4, 127.4, 127.2, 127.1, 120.8, 117.3, 116.8, 110.3, 81.1, 79.5, 68.3, 55.2, 50.1, 28.2, 28.0, 25.8, 18.2, - 5.0, - 5.1; HRMS (FAB) calcd for C₃₇H₅₃N₄O₆Si (M+H) 677.3734, found 677.3762.

Compound 17c: ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 5.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.63 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.21-7.11 (m, 3H), 7.07-7.02 (m, 2H), 5.65 (s, 1H), 5.13 (s, 2H), 2.31 (s, 3H), 1.53 (s, 9H), 1.33 (s, 9H), 0.92 (s, 9H), 0.03 (s, 3H), - 0.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 154.3, 153.8, 147.4, 143.8, 143.4, 137.9, 133.1, 128.3, 128.2, 127.2, 127.1, 123.6, 117.2, 116.6, 81.3, 79.5, 75.6, 50.1, 28.1, 28.0, 25.7, 21.3, 18.2, - 4.9, - 5.0; HRMS (FAB) calcd for C₃₇H₅₃N₄O₅Si (M+H) 661.3785, found 661.3810.

Compound 20a: ¹H NMR (400 MHz, MeOD) δ 8.14 (d, *J* = 5.9 Hz, 1H), 7.85-7.78 (m, 4H), 7.73-7.68 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59-7.54 (m, 2H), 6.83-6.80 (m, 2H), 4.73 (s, 3H), 1.94 (s, 3H); ¹³C NMR (100 MHz, MeOD) δ 196.3, 167.4, 159.3, 148.1, 147.5, 146.5, 136.5, 133.6, 130.0, 128.7, 128.0, 127.1, 114.2, 111.5, 108.7, 44.6; HRMS (FAB) calcd for C₂₀H₁₉N₄O (M+H) 331.1559, found 331.1559.

Compound 20b: ¹H NMR (400 MHz, MeOD) δ 8.07 (dd, *J* = 5.4 and 0.6 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.61-7.56 (m, 3H), 7.39 (dd, *J* = 7.5 and 1.7 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.12-7.08 (m, 1H), 6.82 (s, 1H), 6.79 (dd, *J* = 5.4 and 1.4 Hz, 1H), 4.68 (s, 2H), 3.73 (s, 3H), 1.94 (s, 3H); ¹³C NMR (100 MHz, MeOD) δ 196.8, 167.3, 159.5, 158.2, 148.0, 147.5, 146.6, 133.2, 129.8, 128.0, 127.9, 127.9, 127.2, 120.8, 112.0, 110.8, 108.8, 55.1, 44.7; HRMS (FAB) calcd for C₂₁H₂₁N₄O₂ (M+H) 361.1655, found 361.1675.

Compound 20c: ¹H NMR (400 MHz, MeOD) δ 8.12 (dd, *J* = 5.3 and 0.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.67-7.57 (m, 4H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 6.82 (m, 2H), 4.72 (s, 2H), 2.44 (s, 3H), 1.94 (s, 3H); ¹³C NMR (100 MHz,

MeOD) δ 196.5, 167.3, 159.2, 148.1, 147.4, 146.7, 138.9, 136.5, 134.3, 130.3, 128.6, 128.0, 128.0, 127.4, 127.2, 111.5, 108.7, 44.6, 20.3; HRMS (FAB) calcd for $C_{21}H_{21}N_4O$ (M+H) 345.1715, found 345.1726.